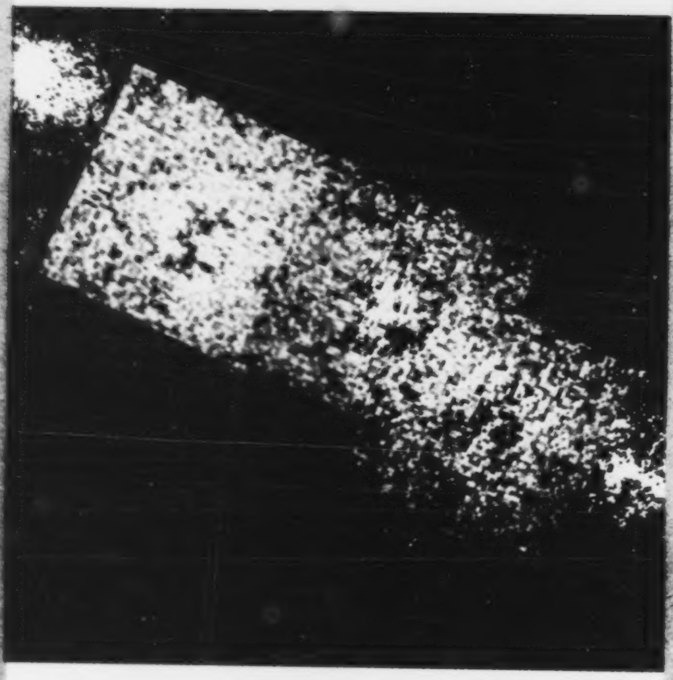
THE ONTARIO CANCER INSTITUTE INCORPORATING THE PRINCESS MARGARET HOSPITAL

1984/85

Clinical and Research Report



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Research Report
1984-1985

The Ontario Cancer Institute
Incorporating
The Princess Margaret Hospital
Toronto, Ontario

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The Ontario Cancer Institute incorporating The Princess Margaret Hospital is Canada's largest centre for cancer research, treatment and teaching. Since it opened in 1958, the OCI/PMH has earned an international reputation for excellence. This Research Review is a report of the research and clinical programs currently in progress.

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AWARDS & HONOURS

Bergsagel DE. The Jeffrey A. Gottlieb Memorial Award of Texas System Cancer Center, University of Texas. M.D. Anderson Hospital and Tumor Institute, November, 1984.

Bush RS. Finzi Lecturer. The Royal Society of Medicine, London, England, April, 1984.

Bush RS. Honorary Membership, European Society for Therapeutic Radiology and Oncology. Stockholm, Sweden, June, 1985.

Cunningham AJ. Ontario Bicentennial Medal, 1984. Awarded by the office of the Premier of Ontario for service to the community through work with evening classes for cancer patients.

Cunningham AJ. Ontario Psychological Association Award, 1985. Awarded for the most innovative clinical program bringing linical psychology to the people and the ommunity.

Fitzpatrick PJ. Testimonial dinner and ward. Laurentian Hospital. Sudbury, Ontario, December, 1984.

Foster FS. Ultrasound in Medicine and Biology Prize. 1984.

Hozumi N. Boehringer Manheim Canada Prize. Canadian Biochemical Society, 1984.

Mak TW. The Outstanding Award of the Year. Chinese Cultural Association of Canada, 1984.

Mak TW. E.W.R. Steacie Award. Natural ciences and Engineering Research Council, Ottawa, 1985.

Mak TW. Ayerst Award. Canadian Biochemical Society, 1985.

Minden MD. Scholar, Leukemia Society of America, 1984.

Rawlinson JA, Bielajew AF, Munro P, Galbraith DM. The Farrington Daniels Award for the best paper on an aspect of radiation dosimetry published in medical physics in the year 1984.

Till JE. University Professor. University of Toronto, Toronto, Ontario, 1984.

Yaffe MJ. Charles E. Ives Engineering Award. Presented by the Society of Photographic Scientists and Engineers, 1984.

Yaffe MJ. Sylvia Greenfield Award. Presented to P. Johns and M. Yaffe by American Association of Physicists in Medicine, July, 1984.

The prestigious E.W.R. Steacie Award was presented to Dr. T.W. Mak by Governor General Jeanne Sauvé at a ceremony in Ottawa.

CLINICAL AND SCIENTIFIC REPORTS

Biostatistics and Methodology

Biostatistical Methodology

D.L. Tritchler, Sc.D., Senior Scientist, Biological Research Division
G.A. Lockwood, M.A., Biological Research Division
R.S. Gelman, Ph.D., Assoc. Professor of Biophysics, Harvard School of Public Health

New methods are being developed for dealing with a variety of data analytic problems arising in biostatistical applications.

The Exact Nonparametric Analysis of A Class of Experimental Designs (Tritchler)
Computational methods based on Fourier techniques have been developed to extend Kendall's rank correlation method to more complex analysis-of-variance designs. This allows more precise analyses of small sets of data, and extends the scope of nonparametric methods.

A Computer Intensive Method for Logistic Regression Sample Size (Gelman, Lockwood, Tritchler)
In biostatistical and epidemiological investigations, the association between a binary response, such as disease or death, and a set of explanatory variables is often studies by multiple logistic regression methods. However, the sample size calculations done to plan such studies typically assume that a simple comparison of proportions is to be done. Methods which have been developed for sample size calculations in the regression framework involve very severe approximations which render them inappropriate for clinical data.

We are currently developing a method which dispenses with the approximations currently used and allows the substitution of prior empirical information for distribution assumptions. The method will provide more realistic estimates of the number of patients needed for a study.

Permutations Tests for Censored Data (Tritchler, Lockwood)
Rank tests for censored data, such as the Wilcoxon-Gehan and log rank tests, have proven invaluable for the comparison of treatment groups in survival studies. These rank methods may be viewed as members of the general class of permutation tests. However, in general, permutation tests have not been extended to the censored data case.

We are currently developing and evaluating extensions of the permutation test to censored data. This may lead to more efficient methods of analysis for various situations.

Conduct and Reporting Methods for Chemotherapy Clinical Trials

I. Tannock, M.D., Medical Oncologist
K. Tonkin, M.D., Resident

This project has involved research into the conduct and reporting of clinical trials of cancer chemotherapy. We have reviewed 62 reports of clinical trials published in major cancer journals between 1980 and the end of 1983. These reports were reviewed carefully for the criteria of response that were used and the completeness of information in the articles. Where this information was not available it was followed by a questionnaire to the senior author and subsequently by a telephone call if no reply was received. On the basis of this research we were able to conclude the following:

a) There is a great deal of heterogeneity in criteria of tumor response that are used in clinical trials that are reported in the literature. This may lead to quite divergent response rates for a common set of data and effectively prevents comparison between different studies.

b) There is rarely sufficient information included in publications which would allow the reader to judge exactly what was done in a particular clinical trial.

Because of these results, and because of our previous results which have shown that measurements of tumors are associated with a high level of measurement error, we suggest that funding agencies and editors of journals should attempt to establish uniform and stringent criteria of response, particularly when reporting Phase III clinical trials that are aimed at judging the benefit to patients of a particular treatment.

Exploratory Analysis and Models for Biomedical Data

A. Ciampi, Ph.D., Senior Scientist, Biological Research Division

The availability of large bodies of data arising from both clinical practice and laboratory experimentation, poses new challenges to the biostatistician. (S)he can often be helpful in testing a hypothesis, or in discriminating between two competing hypotheses. Increasingly, however, the data are of relatively good quality, but prior hypotheses are not available, or are only vaguely formulated: it is then the biostatistician's task to generate hypotheses from the data and/or to turn vague conjectures into testable hypotheses by means of mathematical models.

Regression and Classification in Survival Analysis

In this project we are attempting to improve existing methods for predicting survival of cancer patients from prognostic factors and from treatment information.

The semi-parametric Cox model for regression analysis is considered the "state of the art" in Clinical Biostatistics. However, it is based on assumptions which are not always realistic. In the search for more flexible models, we have proposed a regression model that envisages two possible types of covariate effects (1). Also, we have developed parametric models which allow detailed predictions, such as expected survival, quantiles and survival probabilities at different times, given a number of covariates (2,3).

In order to discover possible interaction effects among prognostic factors, we have continued the development of tree-growing exploratory methodology. A "tree" model allows a very appealing, structured description of distinct prognostic groups. Problems of validity and stability are being investigated. Trees have also been used more recently, to discover groups that may be particularly responsive to a certain treatment (prognostic factor-treatment interactions).

Methods of Analysis in the Study of Quality of Life

In collaboration with Dr. J.E. Till's group, we have continued to study methods of measurement and analysis of data concerning the quality of life of cancer patients.

Since a measurement of life quality involves value judgments, methods of measuring values have been studied. These are based on an adaptation of multivalued utility theory. Measurements have been made possible by the development of an interactive package for micro-computer(s) which elicits values and estimates essential parameters.

Factor analysis and other methods of scale development are being applied to data in order to obtain general health and symptoms scales which will be useful in monitoring patients' health status.

Stochastic Model of Cell Differentiation

Data on cell differentiation arising from cell culture laboratory work may provide useful clues into the biology of tumors. A mathematical model of cell differentiation has been developed, in collaboration with Drs. Buick and Till, which includes as particular cases, submodels corresponding to contrasting biological hypotheses about the dynamics of tumor cell populations. Ontario Cancer Institute data seem to support the stem cell model of cell differentiation against the alternative clonal succession model.

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2. Ciampi, A., Hogg, S.A. and Kates, L. Regression analysis of censored survival data with the generalized F family - an alternative to the proportional hazards model. Stats. in Med. (in press).

3. Hogg, S.A. and Ciampi, A. GFREG: A computer program for maximum likelihood regression using the generalized F distribution. Comp. Prog. in Biomed. (in press).

Clinical Physics

Dose-Response for Radiation Induced Pulmonary Damage

J. Van Dyk, M.Sc., Senior Scientist, Physics Division
T.J. Keane, M.B., Radiation Oncologist
K. Mah, B.Sc., Graduate Student
P. Poon, M.B., Radiologist

Acute radiation pneumonitis and late pulmonary fibrosis are significant causes of morbidity and mortality in the treatment of a variety of malignancies requiring lung irradiation. The degree of damage in either phase will be a function of radiation dose, volume and fractionation. The onset of clinical symptoms is dependent on volume irradiated and the symptoms may range from impaired pulmonary function to death from respiratory failure. While we have accumulated data on the effects of single fraction whole lung irradiation (1,2) accurate information on the nature of the dose-response relationship for acute and late lung damage due to fractionated radiation therapy in man is not available. This has been mainly due to the absence of prospective clinical studies and difficulties in estimating radiation dose in low density lung tissues.

Pulmonary density changes as measured by computerized tomography (CT) after lung irradiation have been shown to be a useful indicator of lung damage (3). A prospective clinical study has been designed to evaluate the tolerance of normal lung tissues to fractionated radiation therapy. Patients who were undergoing radiation treatment of the thorax for various malignant diseases had CT scans of the thorax taken in treatment position and during quiet respiration, before and at specified intervals following fractionated radiation therapy. Since this study is specifically addressing the early phase of lung damage, the follow-up period was from two to six months after the initiation of treatment.

The CT information was used in three ways: a) for precise dose calculations using a CT-aided treatment planning computer, b) for a qualitative diagnosis of radiation damage, and c) for an absolute measure of lung densities as a quantitative diagnosis of radiation damage.

The endpoint for determining radiation induced lung damage was defined as an increase in lung density within the irradiated volume as observed by diagnostic radiologists (Dr. P.Y. Poon, Dr. Rideout and Dr. Jamesky). A typical example of density changes following lung irradiation is shown in Figure 1.

Patients with different fractionation protocols were grouped together according to equivalent biological effectiveness using an estimated single dose model. For each patient the dose distribution was calculated including corrections for inhomogeneities using the equivalent tissue-air-ratio method developed by our clinical physics group.

The preliminary dose-response data for acute lung damage are shown in Figure 2. The steepness of this dose-response curve emphasizes the need for accuracy in clinical dosimetry since a 5% change in dose can result in a 15% change in the incidence of acute radiation induced pulmonary damage.

Further studies are continuing: (1) to assess the relationship between late lung damage and the dose to lung for fractionated therapy, (2) to assess the effects of several commonly used chemotherapy regimens on the dose-response for acute lung damage, and (3) to assess the effects of several commonly used chemotherapy regimens on the dose-response for late lung damage.

The determination of such dose-response data will allow for the optimization of radiation therapy. Furthermore, the comparison of dose-response data for radiation alone to that for combined modality treatments will quantify the relative enhancement of chemotherapy on radiation induced lung damage.

References

1. Van Dyk, J., Keane, T.J., Kan, S., Rider, W.D, Fryer, C.J.H. Radiation pneumonitis following large single dose irradiation: A re-evaluation based on absolute dose to lung. Int. J. Rad. Oncol. Biol. Phys. 7, 461-467, 1981.

2. Keane, T.J., Van Dyk, J., Rider, W.D. Idiopathic interstitial pneumonia following bone marrow transplantation: The relationship with total body irradiation. Int. J. Rad. Oncol. Biol. Phys. 7, 1365-1370, 1981.

3. Van Dyk, J., Hill, R.P. Post-irradiation lung density changes measured by computerized tomography. Int. J. Rad. Oncol. Biol. Phys. 9, 847-852, 1983.

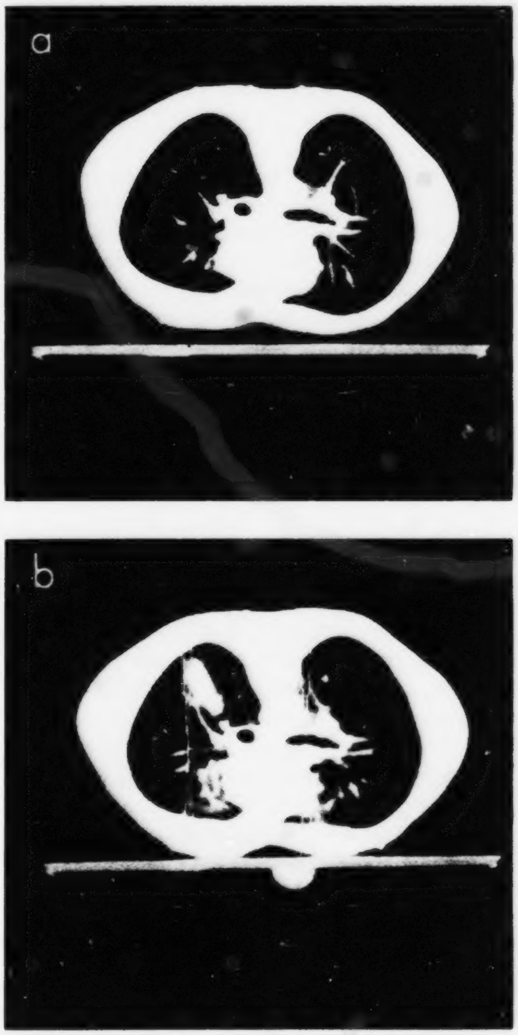

Figure 1. Photograph a) is a CT scan before radiotherapy. Photograph b) is a follow-up CT scan 77 days after the initiation of treatment. Beam edges are displayed on the scan.

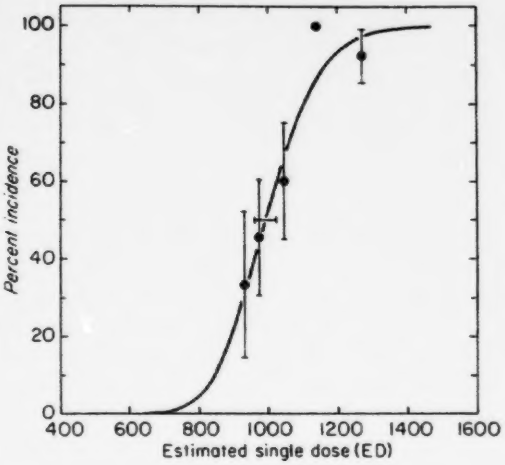

Figure 2. Incidence of acute radiation induced lung damage versus estimated single dose (ED). Error bars are binomial standard deviations.

Equipment Development For Radiation Therapy

J.A. Rawlinson, M.Sc., Physicist, Physics Division
D.G. Galbraith, B.Sc., Physicist, Physics Division
P.M.K. Leung, Ph.D., Senior Physicist, Physics Division
J.R. Cunningham, Ph.D., Chief Clinical Physicist, Physics Division
J. Van Dyk, M.Sc., Senior Physicist, Physics Division
J.B. Grant, M.Sc., Junior Physicist, Physics Division

Each step in the radiation therapy process e.g. diagnosis, localization, treatment planning, treatment delivery etc. requires extensive use of specialized equipment. Frequently suitable equipment is not available commercially and in these cases the appropriate items are often designed and constructed by the Clinical Physics group with the help of The Ontario Cancer Institute's mechanical shop and electronics shop. Here we describe some of the major . equipment under development the use of which we expect will improve the efficiency or precision of the practice of radiation therapy.

Beam Flatness Monitor
The performance of medical accelerators has to be routinely monitored and controlled in order to achieve adequate precision in the delivery of radiation to the patient. One special concern is the uniformity of intensity across the radiation beam. We have designed a matrix dosimeter which allows a rapid yet complete evaluation of the beam flatness of any linac. Our design is especially useful for the current generation of high energy linacs whose electron scanning systems make the use of conventional dosimeters unsuitable. Six units are in use, four on our own linacs and the others at the Toronto-Bayview Cancer Clinic and Atomic Energy of Canada Limited (AECL).

Beam Quality Monitor
A rapid means of quickly assessing the energy spectrum or quality of an x-ray beam from a medical clinic is an important facility, yet current methods are either time-consuming, give ambiguous results or lack adequate sensitivity. We are developing a novel means of quality measurements based on the response of ion chambers in material of different atomic numbers.

3-D Body Contour Digitizer (1)
Knowledge of patient contour and the distribution of internal organs are required for calculating dose distribution where inhomogeneity corrections are necessary. CT scans are a source of this information. For dose distributions not requiring inhomogeneity corrections, the external patient contour is sufficient. The majority of dose calculations for radiotherapy treatment are of the latter group. While the CT scan is a source of patient contour information, it is not necessary or costeffective to use it as such.

We have designed and constructed a system which uses video cameras and the optical range finding principle to take 3-D body contours. The contour sampling, which is done with the patient lying on a couch in a position similar to that of a teletherapy treatment unit, is fast and does not require patient contact. The operation of the unit is controlled by a microcomputer. Data acquired from this system is subsequently uploaded to our treatment planning computer for dose calculation. The system has been completed, and will be installed in our radiotherapy department for clinical evaluation.

Automated Design and Cutting of Compensating Filters (2)
The use of compensating filters in radiotherapy treatments is a routine procedure in many centres. The technique of designing accurate filters is well known, but its precision is limited by the labour intensive and multi-step fabrication procedure. We are currently developing an automated system to design and to cut these filters to a precision which is limited only by the knowledge of dose calculation.

The first phase of development is to incorporate patient information from CT scans or from the 3-D body contour digitizer, into our CT/TP-11 treatment planning system to calculate a compensating filter shape which will achieve the optimal dose distribution. This phase is very near to its completion.

The second phase is to interface our treatment planning computer to our computer-controlled milling machine so that compensating filters can be cut to precision, automatically.

Remote-Controlled Brachytherapy Unit
We have previously shown that radiation exposure from the use of sealed source in brachytherapy is the

major source of personnel exposure, and that remotely controlled brachytherapy unit is an effective means of reducing this source of radiation exposure. Evaluation of commercial units (3,4) shows that none can satisfy our criteria of reliable and safe operation, and flexibility in source loading configuration to meet modern radiotherapy requirements. We have therefore designed and constructed our own using microcomputer controlled pneumatic source transport technology. Two such units have been in clinical use, and two more units are being constructed.

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3. Leung, P.M.K. Personnel radiation exposure analysis in a radiotherapy center: Fourteen year retrospective study. Int. J. Radiat. Oncol. Biol. Phys. *9*: 1705, 1983.

4. Leung, P.M.K. Experience with remote afterloading technique in intracavitary therapy. Int. J. Radiat. Oncol. Biol. Phys. *10*: 157, 1984.

Radiation Dosimetry

J.R. Cunningham, Ph.D., Chief Clinical Physicist, Physics Division
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M. Woo, Graduate Student

Research activities in this group are directed toward the goal of practical improvement of physical aspects of radiotherapy. This includes endeavours that are concerned with improving the accuracy and reliability of radiation dosimetry and radiation treatment planning, the correlation of observed biological effects with radiation dose and the development of equipment and procedures concerned with radiation treatments. It is generally considered, for example, that the dose of radiation delivered in a radiation treatment should be within ±5% of the prescribed dose. This is quite a demanding requirement because many steps are involved. The steps include basic calibration of measuring instruments, quality control of radiation producing equipment, patient dose calculations and quality control of patient positioning for treatment. All of these steps are being examined as part of this project.

Dose Calibrations

The examination and production of data used in absorbed dose calibration procedures has been a continuing concern of the Clinical Physics section. One member (J.R. Cunningham) is a member of a Task Group (No. 21) of the American Association of Physicists in Medicine (AAPM) which has recently produced a protocol (1) for radiation dosimetry procedures for high energy x-rays and electron beams. Much of the basic data used in this protocol was supplied by The Ontario Cancer Institute group. There are still a number of uncertainties concerning the applicability of some of the data however and an evaluation of the numerical values used for the quantities known as mass-energy absorption coefficient ratios and stopping power ratios is being carried out using the Monte Carlo techniques discussed in. Preliminary results suggest that the absorption coefficient ratio varies with the size of the radiation beam and the depth within an irradiated body and that this variation should be taken into account in certain calibration procedures. This is new vnformation.

Charge Effects In Plastic Phantoms

Insulating plastic materials are widely used as a substitute for tissue in radiation dosimetry. We have found that after exposure to ionizing radiation, these materials can accumulate sufficient electric charge to cause large errors in the determination of absorbed dose (2,3). These findings impact significantly on current international protocols dealing with the measurement of dose in radiation therapy. Though our early work was confined to a few specific irradiation conditions, we have recently shown that charge effects can occur over a broad range of situations, including x-ray beams as well as electron beams, and including parallel-plate phantom geometry as well as cylindrical geometry.

In principle, the charge effects can be eliminated by replacing the insulating materials by electrical conductors. However, the use of common insulators such as acrylic or polystyrene is entrenched because of their low cost and excellent dosimetric and mechanical properties. We are therefore exploring the possibilities of reducing charge effects in these materials to tolerable levels.

Monte Carlo Studies For Photon and Electron Beam Dosimetry

An elaborate computer code, known as EGS (electron-gamma shower) which originated at

Stanford University has been obtained and installed on the Physics Division computer system (VAX) with the collaboration of D.W.O. Rogers of the National Research Council. This program predicts the behaviour of radiation beams by calculating and following the individual paths of very large numbers of individual photons and electrons as they interact with an irradiated medium.

This has been implemented as a tool for studying the behaviour of the interaction of radiation with matter and has been applied to: a) the determination of basic radiation parameters (See "Dose Calibrations", above), b) investigations of properties of elemental beams used for patient dose calculations (See "Patient Dose Calculations", below), c) an investigation of dose distributions near tissue inhomogeneities, d) backscattering of electrons by beta emitters (in collaboration with C. Kwok, The Ontario Cancer Treatment and Research Foundation, Hamilton Clinic) and a number of other collaborative projects.

Patient Dose Calculations

The Clinical Physics Group has, over about two decades, developed a number of methods for making dose calculations for radiotherapy which are in routine use throughout the world. There are, however, yet a number of unsolved problems such as how to make accurate calculations for electron beams and for photon beams in regions near interfaces between different absorbing materials. Recent activity in this field has centred on the development and implementation of methods of using elemental or "pencil" beams for making calculations for electrons with an extension of the method to photons. This is a potentially powerful technique. It has recently been recognized that this is a "convolution" procedure for which mathematical and programming techniques have been developed in other areas of physics such as imaging and can be adapted to dose calculation problems.

Brachytherapy Dosimetry

Dose calculation for internal source application requires tissue correction factors similar to the tissue-air ratio in external radiation beam dose calculation. Existing data were obtained from the mean of all available experimental values published in the 1950s. However, values from different authors usually did not agree, and had a spread of more than 10%. The main difficulty for this type of measurement was to establish proper correction factors for ionization chambers when they were used to measure dose at short distances from the source.

Preliminary work has been carried out using Monte Carlo calculations in the hope of generating better tissue correction factors. It is also possible to calculate ionization chamber corrections under different experimental conditions so that direct experimental verification of the calculated values can be made. When a set of good tissue correction factors is available, inhomogeneity correction methods for brachytherapy can be explored.

The Dosimetry of Half Body and Total Body Photon Irradiation

The use of half body and total body radiotherapy has increased over the last few years both for the palliation of metastatic disease and in conjunction with bone marrow transplants for leukemic and anemic patients. Because of the large radiation fields needed for such treatments, the dosimetric uncertainties are much more pronounced than they are for conventional field sizes. Large field radiotherapy has become increasingly popular on a world wide scale; hence, it is imperative that the dosimetry is accurately controlled so that clinical results from different institutions can be compared. To this end, the various parameters affecting dose delivery are being evaluated. Furthermore, one of us, (J. Van Dyk) is involved in a Task Group for the American Association of Physicists in Medicine (AAPM) to provide recommendations regarding dosimetric procedures that should be used prior to initiating large field treatment procedures.

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Experimental Therapy

A Comparison Of Sustained Release Morphine Sulphate Tablets With Standard Morphine Oral Solution

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Despite the availability of potent analgesics, pain in cancer patients is often poorly controlled. There are many reasons for this lack of good symptom relief, but a frequently quoted one is the failure to adhere to regular (rather than PRN) morphine administration every four hours. The necessity of six doses per day discourages patient compliance and hence contributes to suboptimal pain control.

Recently a sustained release morphine preparation that can be administered twice daily has been developed in Europe. Uncontrolled trials have suggested that this new formulation is as efficacious as morphine syrup. Because these studies were anecdotal, unblinded or had other methodologic problems, the results are difficult to interpret. A double-blind, randomized cross-over trial has, therefore, been initiated at three Canadian oncology centres. Patients with pain due to cancer will be given a seven-day trial on each medication with daily assessment of pain and side effects. The study is ongoing and results are not yet available. If the new formulation has equivalent efficacy and side effects, it will replace morphine solution as the cornerstone of analgesic therapy for severe pain.

Basic Studies In Hyperthermia

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Interest in heat treatment (hyperthermia) given either alone, or in combination with radiation or chemotherapy, has been rekindled recently as a viable approach in cancer treatment. Experimental studies with cells in culture have demonstrated the cell-killing potential of heat particularly for cells resistant to radiation due to hypoxia, and studies in animals have shown that some tumors can be cured by a combination of heat and radiation treatment. Early clinical studies have demonstrated good responses in a number of different types of human cancers. Although hyperthermia has considerable promise, many physical and biological problems must be solved before hyperthermia can be applied routinely and reliably in the clinic (1). Two crucial problems are being investigated in our laboratory. The first is to develop hyperthermia sources that can generate well-defined heating distributions in a deep-seated tumor, yet with minimal heating to the neighbouring tissues. The second is to study the effect of heating on blood flow in tumors and in normal tissues.

Ultrasound Hyperthermia Sources (Hunt, Hill, Lockwood, Taylor, Worthington)

Ultrasound (U/S) has considerable physical advantages over other heating modalities since the beam can be focussed effectively to give heating at depth in the body. Furthermore, various sizes and shapes can be obtained. However, ultrasound is limited to the soft tissues of the body, since there is little penetration through air or bone.

Several ultrasound heating sources have been developed. One is a 1.6 MHz surface heater with a plasma transducer which produces heating distributions of 4 cm to 7 cm in diameter, and a useful penetration depth of 2 to 3 cm (2). By cutting the transducer into an annular array, better heating distributions have been obtained. Several novel transducer systems containing a double-reflecting cone or a conical lens system are currently being studied. These produce an intense line-focus that is projected into the body. By various mechanical scanning techniques, excellent heating distributions have been obtained in the laboratory and these systems will be tested in large animals.

Unfortunately, the ultrasound beams interact with currently available temperature probes and thermometry systems. Consequently a sixteen-channel digital thermometry computer interface has been developed in which the computer interrupts the beam while the temperatures are read. The accuracy of this system is ^{3}0.1 °C.

Experimental Neurooncology: Interstitial Radiation and Hyperthermia In The 9L Rat Brain Tumor Model (Hunt, Bernstein, Brown, Worthington)

Malignant brain tumors are essentially localized to one area of the brain at the time of diagnosis and distant metastases are rare. Therefore, the challenge is to cure these fatal tumors by local treatments. The mainstay of adjuvant therapy (after surgery) is irradiation, but the brain's tolerance to radiation is limited and often tumors recur or fatal radiation necrosis is found. Local hyperthermia treatments may have the potential to improve this situation. The project is to explore the use of hyperthermia by itself, or in combination with high-activity implantable and removable ^{125}I seeds using a rat brain tumor model. Various heating techniques are being examined and at present, the best heating distribution has been obtained with an rf induction technique using a pancake shaped coil excited by a 28 MHz radiofrequency power source. When satisfactory heating distributions have been achieved, the survival and pathology of animals containing implanted 9L rat brain tumors will be studied after various treatments.

Blood Flow Experiments (Brown, Hunt, Hill)

Blood flow is the major cooling mechanism in heated tissue and in response to higher temperatures in the body, blood flow can increase. Studies by other workers have suggested the blood vessels in tumors do not respond as effectively as those in the neighbouring normal tissues. Thus tumors may reach higher temperatures during treatment since the blood flow cooling is less.

This program is to test the blood flow of both tumor and normal tissue during hyperthermia treatments over a range of temperatures and heating times. The normal tissue studied will be the leg muscle of a C3H mouse, and the tumors will be the KHT fibrosarcoma and a mouse mammary carcinoma both growing in the leg. The efficacy of tumor treatments will also be assessed by using cell survival and tumor growth delay assays.

Uniform heat treatments are accomplished using simultaneous radiofrequency (13.56 MHz) capacitive and saline bath heating based on a design by Joiner (Br. J. Cancer, 45, Suppl. V:71, 1982). A 16-channel thermometry system featuring type K thermocouples which are approximately 35 μm in diameter, has been constructed and optimized. Temperature measurements are monitored by an Apple IIe microcomputer. Initial measurements suggest that the system is capable of heating a 1.5cc volume at a uniform temperature (for example 42.0°C) with an accuracy of ^{3}0.1°C.

Blood flow (BF) is determined by the rate of clearance of a radioactive tracer either xenon gas (4) or pertechnetate ion. This method gives a dynamic measure of BF which does not require sacrifice of the animal. Sodium pertechnetate (Na ^{99m}Tc O_4) is a desirable tracer because it has a relatively short half-life (6 hrs), low principle energy (142 keV), and is readily available at minimal cost. Clearance rates of Na ^{99m}Tc O_4 and Xenon (^{133}Xe) were compared following a dual injection in mouse muscle and tumors of various sizes. Clearance rates of Na ^{99m}Tc O_4 in mouse muscle compared favourably to ^{133}Xe. However, in KHT Sarcomas the rate of clearance of ^{133}Xe was consistently faster than that of Na ^{99m}Tc O_4. This data suggests that Na ^{99m}Tc O_4 is not as freely diffusible as ^{133}Xe and that the rate of clearance of Na ^{99m}Tc O_4 in tumors reflects both BF and tissue transfer properties (i.e. diffusion, capillary surface area, etc.).

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Causes of Cell Death in Solid Tumors

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In our research into causes of cell death in solid tumors, we have found that neither hypoxia nor acidic conditions along are toxic to cells in culture but a combination of these conditions (as is known to occur in solid tumors) is highly toxic to cells. We have also used the spheroid model to study the effect of limited diffusion of other nutrients and these studies suggest that limited diffusion of glucose but not of glutamine may also be important in causation of cell death. Our studies suggest new methods for trying to kill tumor cells. The environment in solid tumors is known to be acidic and viability of cells is therefore dependent upon a cell's ability to protect itself against the acidic environment. Some drugs are available which limit the ability of a cell to extrude hydrogen ion in exchange for other ions and we have shown that some of these drugs are toxic to cells under acidic conditions. We are extending these studies to the use of spheroids as a solid tumor model and to study effects against tumors in animals. We are also studying mechanisms of cellular death, particularly by evaluating intracellular pH fluorometric methods.

Pharmacology Of Antineoplastic Agents

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The work in this area approaches antineoplastic pharmacology at two levels - clinical studies of chemotherapeutic agents and experimental pharmacology. This two level approach fosters a means by which questions and suggestions can flow between the laboratory and the clinical setting. Although chemotherapy has contributed to the cure of some malignancies and the palliation of many others, the toxicities of the drugs and the resistance of solid tumors in particular to such treatment makes it encumbent on pharmacologists to develop drugs which have decreased toxicity and increased efficacy, i.e. an improved therapeutic index.

Clinical Pharmacology (Rauth, Soldin, Theissen)

We have applied the principles of clinical pharmacology to antineoplastic agents currently in use in the clinics to determine: 1) the relationship between drug pharmacokinetics and clinical toxicity, and 2) the pharmacokinetics of agents in greater detail so that new methods of drug administration can be designed. To this end we have completed the clinical pharmacokinetic studies of mitomycin-C, cyclophosphamide, cisplatin and 5-fluorouracil by continuous intravenous infusion. Our studies of mitomycin-C determined that plasma terminal half-life, C x T and drug clearance did not relate to clinical toxicity. Studies using high pressure liquid chromatography and a sensitive bioassay did not reveal a toxic metabolite for mitomycin-C not detected by the chromatographic technique. The studies of cisplatin and cyclophosphamide allowed us to develop a sensitive assay for cyclophosphamide and to determine the drug disposition and urinary excretion on two consecutive courses. 5-Fluorouracil studies were performed in the context of a Phase I study of 5FU and allopurinol to determine whether non-linear kinetics of this drug could be detected. The clearance and steady state plasma levels of 5FU increased linearly with dose and no saturation was detected.

Our future studies will be directed to determining antineoplastic drug interaction in combination chemotherapy, variation in drug disposition between patients and variations in drugs courses to course. In conjunction with Dr. Kerr at the Toronto Bayview Cancer Clinic, a one year Clinical Pharmacology-Oncology Residency program will be offered for one individual yearly starting July 1985.

Experimental Pharmacology

The research in the laboratory has been directed towards resistance to antineoplastic drugs by solid malignancies. Two specific issues with regards to resistance are addressed - drug penetration into solid tumors and DNA repair as a means of overcoming antineoplastic cytotoxicity.

Drug penetration into solid tumor nodules may be restricted, therefore, limiting cytotoxicity. We have developed the MGH-U1 spheroid model for *in vitro* study of solid tumors. This cell line derived from a bladder tumor has been characterized in terms of its growth and histological appearance when maintained as spheroids and then used to study the effects of adriamycin, epirubicin, cisplatin and carboplatin. Currently, studies of 5FU, methotrexate, vincristine and mitomycin-C are underway. We study the drug cytotoxicity using a colony-forming assay, as well as studying growth delay in spheroids and the effects of drug in immune-deprived mice bearing MGH-U1 solid tumor nodules. These studies have demonstrated that penetration is a problem for some agents, e.g. adriamycin, but not others, e.g. cisplatin.

DNA repair which may occur in cells in response to damaging agents may be important in overcoming the injuries to DNA caused by antineoplastic drugs. This is being assessed by determining the effects of an inhibitor of the enzyme poly(ADP-ribose) synthetase (a nuclear enzyme involved in DNA synthesis) on the cytotoxicity of cisplatin and bleomycin. Studies of antineoplastic drugs and inhibitor to date have demonstrated increases in cytotoxicity in EMT/6 murine fibrosarcoma cells when compared to antineoplastic drugs alone. Future studies will be designed to determine the effect on DNA of such *in vitro* treatments.

The studies in our laboratory are designed to address questions of clinical relevance in the antineoplastic drug treatment of solid tumors. Such studies may define new approaches to chemotherapy which may be clinical useful in the future.

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Radiation-Drug Combinations For The Treatment Of Solid Tumors

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The combination of partially effective treatment modalities in order to improve current cancer treatment regimes remains a major challenge to oncologists. In particular, we are studying several drugs that are currently being used clinically in combination with radiation in experimental model systems in order to better understand their mechanism of action and to develop new rationales for how they may best be combined. This work has been aided by discussions with a number of our clinical colleagues in radiation and medical oncology.

The Study of Nitroimidazoles as Agents with Selective Toxicity Towards Solid Tumors (Laderoute, Lapointe, Sochor, Rauth)

As tumors grow, they may outgrow their vascular blood supply and contain regions in which oxygen is at low levels. Cells in such regions are radiation-resistant. Nitroimidazoles can selectively sensitize oxygen-deficient cells to radiation without altering the sensitivity of cells with a good oxygen supply, such as normal cells. In addition, due to the localized metabolism of nitroimidazoles in cells at low oxygen levels, this class of compounds has shown selective toxicity towards hypoxic cells (1).

We are continuing our studies on the mechanism of action of this selective toxicity at the level of the detailed chemistry of the drug alterations that occur. This work has been done in collaboration with Dr. R.A. McClelland of the Chemistry Department at the University of Toronto. We have succeeded in identifying and in some cases isolating a series of metabolites of the nitroimidazoles from model drug reduction systems. This work suggests that a short-lived reactive species may be involved in the action of these compounds (2). Such a reactive species supports the suggestion of others that this class of compounds may be useful as markers for the presence of hypoxic cells in tumors. These basic chemical studies have also shown that different levels of oxygen are required to block the metabolism of different types of nitroimidazoles suggesting the usefulness of these drugs as probes for the degree of hypoxia in different tumors (3). Dr. H.B. Michaels of the Toronto-Bayview Clinic has also been a collaborator on aspects of this work on oxygen inhibition.

Mitomycin C as a Hypoxic Cell Specific Agent (Marshall, Rauth)

The cancer chemotherapeutic agent mitomycin C has been widely used for the treatment of a variety of solid tumors. It has been shown to have increased toxicity toward hypoxic cells compared to aerobic cells in tissue culture and this is postulated to be due to the enzymatic activation of these compounds to an intermediate chemical species whose ultimate fate is oxygen sensitive. We have been involved in developing a technology which allows us to monitor the effect of oxygen on the toxicity of mitomycin C in a tissue culture system *in vitro*. The oxygen probe used to measure oxygen levels in solution is sensitive to oxygen at levels 1/10,000 that in air-equilibrated solution. It was developed by Dr. C. Koch of the Cross Cancer Institute in Edmonton, with whom we have also collaborated in the evaluation of this new probe. Using this probe we have been able to demonstrate that at least two mechanisms exist for activating mitomycin C, one which is oxygen sensitive and one which is oxygen independent. The role of these two mechanisms can vary from one cell type to another and can be independently modified by the presence or absence of vitamin C. These studies suggest new variables that may be important to the use of these drugs clinically.

In collaboration with Dr. C. Erlichman of our Institute, we have developed a biological assay for active drug in plasma of patients who are undergoing mitomycin C chemotherapy for recurrent metastatic colon cancer. This assay is relatively simple, sensitive and accurate and may be useful for measuring the level of activity of a variety of alkylating agents of use clinically. Such an assay can measure the activity of the parent drug and also the presence of unknown active metabolites and may be useful for predicting drug side effects in patients undergoing chemotherapy.

The Use of Infusional 5-Fluoruracil with Fractionated Radiation for the Treatment of Squamous Cell Tumors (Weinberg, Lapointe, Rauth)

Many patients with squamous cell tumors of the head and neck, anus and cervix are being treated in our Institute with 5-fluoruracil given with fractionated radiotherapy by continuous i.v. infusion. In order to investigate this treatment scheme in more detail, we have established a model system in which mice bearing a transplantable squamous cell tumor in their leg can be given infusional 5-fluoruracil using a mini-osmotic pump and localized fractionated radiation. Using daily doses of radiation of a size used clinically, we have found that infusional 5FU potentiates the effects of this radiation by delaying tumor regrowth to a greater degree than does sn acute single dose of radiation. The present model system will be useful for comparing the effects of altering the time sequence as well as the dose of 5-fluoruracil to be combined with ionizing radiation and for investigating new drug-radiation combinations.

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Health Status and Mental Adjunctive Therapy

Assessment Of Health Values

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With the many changes in health care, health-related decisions are becoming more complex than they were in the past. In part, the myriad of choices is a result of advances in technology, but moral concerns and values are also involved. Examples of the latter are differences in views about the goals of health care and how they should be reached, including such issues as the competency or willingness of patients to become involved in decisions about their own care. Interest is growing in the use of decision aids designed to help patients and health professionals to sort out the different factors involved in health-related decisions. A long-term goal of this research is the development and evaluation of such decision aids.

Assessment of Values in Laryngeal Cancer (Llewellyn-Thomas, Sutherland, Ciampi, Etezadi-Amoli, Boyd, Till)

Although quantitative estimates of patients' attitudes toward the relative importance of different aspects of health are of great potential usefulness in medical decision making, there is little information about the stability of such values over time, particularly in patients whose clinical state is changing.

To examine these questions, we selected a group of patients with laryngeal cancer undergoing treatment with radiotherapy. In this group of patients clinical problems are relatively circumscribed and related to the voice, and a temporary deterioration in voice-related symptoms and abilities is expected during treatment. Thirty patients were interviewed at the start and completion of a month's course of treatment. At each interview patients rated the quality of their own voices using a number of visual analogue scales and also provided both holistic and decomposed quantitative values for the importance of different aspects of voice function and sound.

Although the analogue scales demonstrated the anticipated deterioration in the quality of the patients' voices, these changes in clinical state were not accompanied by any changes in the values of patients assigned to each aspect of voice sound and function.

These results indicate that at least in the short term the values expressed by patients appear to be stable and uninfluenced by changes in their own clinical state (1).

Eliciting Preferences For Alternative Drug Treatments (O'Connor, Boyd, Tritchler, Kriukov, Sutherland, Till)

The purpose of this project was to examine some methodological problems associated with the elicitation of preferences. The project was part of a larger study designed to develop improved strategies for explaining treatment decision problems to patients, with particular emphasis on helping patients to choose between alternative therapies in ways that are consistent with their preferences. Preferences for alternative drug therapies were sought from 208 visitors to an Open House at The Ontario Cancer Institute incorporating The Princess Margaret Hospital, and from 216 University of Toronto nursing students. Preferences were not found to be significantly dependent on the age, sex or professional status of the respondents, nor on the means used for elicitation of preferences (a computer terminal versus a pencil-and-paper questionnaire). In contrast, the importance of the way decision problems are presented ("framed") was confirmed. Use of a negative frame (outcomes of treatment expressed as probability of dying) yielded responses different from those obtained for a positive frame (outcomes expressed as the probability of surviving). A comparison of positive and negative frames with a mixed frame (probabilities of surviving and dying were both given) pointed to the negative frame as the main source of "framing bias"; respondents' preferences were sensitive mainly to the presence or absence of the word "survive" in the outcome description (2).

Eliciting Values For Health States (Till, Ciampi, Llewellyn-Thomas, Sutherland)

In oncology, where increasing numbers of alternative therapies are becoming available, and where patient preferences among these alternatives are becoming increasingly important, reliable and valid information about quality of survival can seldom be provided (3). The problem of measuring quality of survival is inextricably linked to the problem of measuring values, since the impact of changes in a patient's health status may be expected to be dependent on that patient's value system. Values are equally important in decisions. When treatments differ in their consequences, individuals with different value systems will rank them differently in terms of desirability, and for this reason will make different choices. Work is currently under way to test whether or not values may differ between different groups of patients with breast cancer, and how they may be related to the patients' own health status. Future work will continue to emphasize the centrality of value differences among patients.

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Influence Of The Mind On Cancer

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Evidence That The Mind Affects Cancer

The strength of the argument for a mind-cancer link lies not in any one experiment or even any one field of research, but in the convergence of evidence from three quite separate areas: animal experiments, human personality studies and clinical trials. Animal studies show that a variety of stressors can increase the incidence and rate of growth of cancer, while an ability to control the stress diminishes rate of growth in some experiments. Recent work demonstrating an effect of psychological state on the immune response suggests a possible pathway through which the mind may influence cancer: mental attitude or expectancy hormonal response immune depression cancer growth. The large literature correlating personality in humans with risk of acquiring cancer implies that risk may be increased by lack of closeness to parents early in life, by depression, repressive tendencies, non-assertiveness and possibly by recent loss of an important relationship. A number of clinical trials claim prolongation of life in cancer patients given various kinds of psychotherapy; while these were mostly uncontrolled studies, one randomized controlled trial claimed a positive effect for cognitive behaviour therapy, while another with a case-controlled design showed no prolongation of life from attendance at a psychosocial support group.

Current Project

Our research aim is to test the ability of a brief group behavioural therapy programme (teaching "self-help" techniques), (a) to improve mood (relieve anxiety and depression), and (b) to prolong life.

At The Ontario Cancer Institute incorporating The Princess Margaret Hospital, we have developed a program which includes the kinds of intervention claimed by others to be useful in helping to combat cancer: relaxation, meditation, mental imagery and self-awareness (e.g. how to handle stress, and defining and working towards goals). These techniques are all in fairly general use by clinical psychologists and psychiatrists, the only somewhat radical element being the use of visualization of tissue changes. Our patients have all received regular medical treatment. Groups of about 10 people meet for 1 1/2 hours per week for seven weeks, and individuals do considerable home practice with the aid of audiotapes. Follow-up discussion and support groups are held for "graduates" of the course, and more advance groups are being instituted.

Over the last three years, 130 patients, plus a small number of spouses and health professionals, have taken the course. Attendance rate (over 80%) and compliance with the homework, has been high. Our first aim has been realized: this kind of therapy alleviates psychological distress, especially anxiety and depression, as is shown both clinically and from the results of standard questionnaires given before and after the course. The next step is to compare the behavioural program with a support group control in a randomized way: the first cohort of patients to complete these parallel groups showed a decided preference for the behavioural "self-help" therapy. We will be extending this investigation, and also looking at long-term follow-up.

Testing the more radical hypothesis, (b), that this kind of therapy may prolong life, will require the recruitment of patients with relatively homogeneous disease into randomized therapy versus control groups. It is our preliminary impression that patients who do well medically are often among those most involved with their meditation and imagery. The major stumbling-block to proving a causal connection is that only a small proportion of people are sufficiently motivated to do enough work to have a chance of making observable differences to their disease. We are about to introduce, after having pretesting them, more advanced, structured courses in psychological selfhelp which may assist more patients to progress further.

Theoretical Work

In parallel with the more practical group work, an attempt is being made to develop a simple theoretical scheme which will rationalize the effects of psychological, social and spiritual/existential levels of stimuli in health and disease. Interaction between levels of an individual may be most helpfully viewed in terms of information transfer, rather than as specific mechanisms. The central idea is that adequate information "flow" between levels, eg. between the various levels of the body and conscious and unconscious mind, and between mind and social levels, is essential for maintenance of health. The mode of therapy that we are testing may be conceptualized as an attempt to promote optimal information flow or "connectedness" between the many organizational levels of the person.

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Imaging

Breast Imaging

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Mammographic Signs and Breast Cancer Risk

We have carried out a case-control study to examine the relationship between mammographic signs and breast cancer. The mammographic signs assessed were prominent ducts and dysplasia.

The cases were a group of 183 women with histologically verified unilateral breast cancer. The controls were a group of women attending a screening centre. Cases and controls were individually age-matched. Mammograms from the non-cancerous breast of the cases were randomly assembled with those of the controls and classified by three radiologists without knowledge of which films were from cases and which from controls.

Mammographic dysplasia was found to be strongly associated with breast cancer, particularly in women aged less than 50. Prominent ducts were only weakly associated with breast cancer. Multivariate analysis showed the association between dysplasia and breast cancer, and that classification of dysplasia discriminated more strongly between cases and controls than did classification with Wolfe's mammographic patterns.

These results show that mammograms contain information about risk of breast cancer. Mammographic dysplasia is strongly associated with breast cancer, is present in a substantial proportion of patients with the disease, and may offer opportunities for prevention.

Mammographic Patterns and Breast Cancer Risk: Methodologic Standards and Contradictory Results

The claim that classification of the pattern of the breast parenchyma upon mammography can distinguish groups at different risks for breast cancer has been examined by 17 other studies published in the English language literature with contradictory results; this controversy was assessed by us in examination of these studies for their adherence to commonly accepted methodologic standards for the investigation of causal relationships. The nine standards for the examination of the studies included a description of the way the study population had been assembled and followed up and descriptions of the methods of mammographic pattern classification and breast cancer risk analysis. A strong association was found between the standards adopted by a study and the obtained results. Among nine cohort and case-control studies that found a statistically significant association between mammographic pattern and breast cancer risk, all met at least four standards, whereas only two of six "negative" cohort or case-control studies met as many as four standards. Among prevalence surveys, the association between methods and results was less striking, but several negative prevalence surveys were associated with "positive" cohort studies employing the same group of patients. These results indicate that methodologic differences among studies contribute substantially to the controversy surrounding this subject. Studies that follow the usual scientific methods employed in the epidemiologic investigation of risk generally have confirmed an association between mammographic pattern and breast cancer risk.

Correlation of Mammographic Patterns and Breast Ultrasound Images

Although mammographic signs in the breast parenchyma appear to be associated with breast cancer risk, there is little information available about the prevalence of dysplasia or other changes in the breast parenchyma in populations at different risks for breast cancer. To examine this question it would be necessary to have available a method of imaging the breast that was risk free, so that it could be applied to healthy members of populations, and portable. Unlike mammography, breast ultrasound does meet these criteria. In collaboration with the Breast Ultrasound Group at The Ontario Cancer Institute incorporating The Princess Margaret Hospital (Drs. Hunt and

Foster), and the Department of Radiology at Women's College Hospital (Dr. E. Fishell), a study is in progress to correlate the mammographic appearances of the breast parenchyma and the density of the breast on ultrasound examination. Possible future applications of breast ultrasound in this context include not only the study of populations, but following at close intervals changes in individuals undergoing dietary intervention.

Sources of Variation in the Magnetic Resonance Image of the Breast

Because it seems likely that the radiologic appearance of dysplasia is due to the ratio of fat to water in the breast, an imaging modality that provided quantitative estimates of these properties would be useful. Magnetic resonance imaging (MRI) has the ability to estimate ratios of fat to water, and a preliminary study has been undertaken in collaboration with the MRI group at The Ontario Cancer Institute incorporating The Princess Margaret Hospital (Drs. Henkleman, Bronskill, Poon and Rideout), to examine the reproducibility of MRI images at different times in the menstrual cycle in premenopausal women, and on different occasions in postmenopausal women. Women in whom mammographic images have been obtained will be recruited from the Women's College Hospital and The Princess Margaret Hospital, and the MRI image correlated with the mammographic appearance of the breast.

The False-Negative Mammogram

Little systematic attention has been paid to understanding the failure of mammography to visualize some breast cancers, and previous work on the subject has been concerned chiefly with technical reasons for a false-negative image. To examine the possibility that there may be biologic differences between cancers that are visible mammographically and those that are not, we have, in collaboration with the Department of Radiology (Dr. E. Fishell), and the Department of Pathology (Dr. W. Hanna) at Women's College Hospital, reviewed the 500 breast cancers diagnosed at Women's College Hospital from 1978 to 1983. These cancers have been classified according to whether or not radiologic evidence of malignancy was present at the time of diagnosis. All films that did not show evidence of malignancy on mammography, and a randomly selected equal number of films that did show signs of cancer have been assembled, and admixed with a predetermined number of films from normal subjects. Re-reading of these films without knowledge of their original classification has shown a striking consistency of interpretation. Analysis is now underway to compare individuals in whom true-positive and false-negative images were obtained with respect to their clinical and epidemiologic characteristics, tumor pathology, and oestrogen receptor status as well as the general radiologic characteristics of the breast.

Correlation of Breast Histology and Radiology

Although previous workers have described an association between presumed premalignant histologic changes in human breast tissue and mammographic dysplasia, independence of classification and freedom from possible biases in the selection of the material was not assured.

To examine the histologic changes in the breast epithelium associated with mammographic dysplasia we selected a consecutive series of patients, aged less than 50, who had undergone mammography and surgical biopsy of the breast. Patients with invasive cancer were excluded. Mammograms and histologic slides were assembled for 175 subjects and classified independently. The proportion of the breast occupied by the radiologic changes of dysplasia was determined by two radiologists and the histologic classification of epithelial atypia verified by three pathologists.

A strong and statistically significant relationship was found between the presence of epithelial atypia and the proportion of the breast occupied by radiographic dysplasia. Further, among patients with atypia, the number of affected lobules was also significantly related to the extensiveness of radiologic dysplasia. These results thus show evidence of a quantitative relationship between histologic and radiologic indicators of breast cancer risk; however, the assembled material contains few subjects in low risk radiologic categories, and few in the high risk histologic categories of carcinoma in situ or marked atypia. To overcome these deficiencies, and to allow an examination of the association of both radiologic and histologic indicators of risk with other risk factors for breast cancer such as reproductive variables and indices of body size information from a larger number of subjects is presently being collected. as reproductive variables and indices of body size information from a larger number of subjects is presently being collected.

Diagnostic Imaging Department

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The Department of Diagnostic Imaging provides services in conventional radiology, computed tomography, ultrasound, thermography and magnetic resonance imaging.

Conventional radiology which includes such specialized procedures as lymphography and myelography is stable in total volume at 35,512 examinations during the year. There has been a moderate increase in the number of requests for mammography.

The demand for ultrasound service is rising slowly and reached 979 examinations during this year. This does not include a substantial number of examinations performed for research purposes.

The volume of thermograms has not changed significantly although there has been an increase in clinical interest in the use of this modality to evaluate chronic intractable pain.

The demand for computed tomography is levelling off at 5,964 examinations during the year. There has in addition been substantial use of the equipment in research protocols and together these uses require approximately eighty hours of machine operating time per week. The potential for use of a single CT installation is now virtually saturated.

Magnetic resonance imaging has begun operation as a service modality with a potential for 1,500 examinations per year. It will, in addition, be used extensively in research protocols.

Clinical Research Activities In The Department Of Diagnostic Imaging

Ultrasound

Three research projects are in progress in this area. Real time sonography of cancer of the cervix by Dr. Blend in collaboration with Dr. G. Thomas of the Department of Radiation Oncology. These results were presented at the Canadian Association of Radiologists meeting in June 1985. Dr. Blend is collaborating with Dr. W.B. Taylor of the Department of electronics and Dr. Hunt, Department of Physics in the development of a real-time axial transrectal ultrasound probe which will be used particularly in examination of the prostate. thirdly, evaluation of the latest prototype of breast ultrasound in proceeding in conjunction with Dr. Hunt, Dr. Stuart Foster and Mr. Taylor.

Computed Tomography

A study of the value of CT in staging of primary rectal carcinoma and detection of recurrent tumor after resection is proceeding in collaboration with Dr. B. Cummings, Dr. T. Keane, Dr. A. Harwood, Department of Radiation Oncology and Dr. K. Li, Radiology Department, St. Michael's Hospital.

A biomechanical analysis of diaphyseal fractures in metastatic cancer is proceeding under a grant from the Wellesley Hospital Research Institute. The investigators are Dr. P.Y. Poon, Dr. J.R. McBroom, D.W.C. Hayes, Dr. B.L. Fornasier and Dr. M. Clark.

A prospective clinical study has been conducted to determine the incidence of acute postirradiation pneumonitis after fractionated radiation treatment in collaboration with Miss K. Mah and Mr. J. Van Dyk of the Clinical Physics Department and Dr. T.J. Keane, Department of Radiation Oncology. The investigators from the Department of Diagnostic Imaging are Dr. P.Y. Poon, Dr. I.F. Majesky and Dr. D.F. Rideout. Fifty patients were studied. The dose response curve predicts a 30 per cent increase in the incidence of acute postirradiation pneumonitis for a 10 per cent increase in dose. Observer variation in abdominal CT has been studies by Dr. Herman, Dr. Majesky, and Dr. Rideout in collaboration with Dr. DeBoer of the Department of Biostatistics.

An evaluation of CT in ovarian cancer has been undertaken by Dr. Herman, Dr. Rideout, Dr. Majesky in collaboration with Dr. Warr, Dr. Boyd, Dr. Sturgeon, and Dr. Fine. This work has been presented at the American Federation for Clinical Research, Philadelphia, October 1984 and the Radiological Society of North America, Washington, November 1984.

Conventional Radiology

Factors predicting success or failure in lymphography were analysed in a prospective study of 150 consecutive patients by all members of the Department staff and the results presented at the Canadian Association of Radiologists meeting, Vancouver, June 1984.

Dr. Rideout collaborated with the testicular tumor group in a study of surveillance after orchidectomy for non-seminomatous testicular tumors which is to be presented at the meeting of the Royal College of Physicians of Surgeons of Canada.

Magnetic Resonance Imaging

Dr. Poon participated in an evaluation of magnetic resonance imaging in oncology in collaboration with the MRI evaluation steering group. The studies are in a final stage and the data is being analyzed. Other members of the Department have participated in research projects connected with MRI as follows: Dr. Majesky in evaluation of MRI in detection of brain metastases; Dr. Blend in evaluation of MRI in spinal cordlcompression; Dr. Rideout in evaluation of MRI in detection of mediastinal involvement in bronchogenic carcinoma.

Additional minor studies which have either been completed or are in progress of completion by Dr. Poon, the Steering Group and participants from other hospitals within Toronto include; evaluation of MRI in orbital tumors, knee joint, soft tissue tumors of the extremities, avascular necrosis of the hip, focal epilepsy, retroperitoneal lymphadenopathy, and bladder tumors. Dr. H. Dunlap has participated as a research fellow in the MRI projects.

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Magnetic Resonance Imaging

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Magnetic Resonance (MR) Imaging is evolving rapidly in the 1980s as an exciting imaging modality of great promise. The basic technique consists of placing a patient in a homogeneous magnetic field within the bore of a large magnet. Time-varying magnetic field gradients and radiofrequency pulses are used to generate variously-encoded MR signals from mobile protons in different parts of the body. Computer imaging techniques are then used to calculate and display, through the patient, two-dimensional gray scale images of sections that are typically 256 x 256 pixels in a single plane. The spatial resolution achieved is similar to that of x-ray computed tomographic imaging (CT) which is the most comparable competitive imaging modality, and excellent contrast is obtained between various types of soft tissues.

MR images differ significantly from x-ray images because the gray scale exhibited depends on multiple parameters, which are properties of the tissue imaged and type of MR experiment performed.

MR Image Parameters

Properties Of The Patient	**Adjustable Imager Properties**
p - proton density	TE - echo time
T_1 relaxation time	TI - inversion time
T_2 relaxation time	TR - repetition time
motion and/or flow	k - receiver sensitivity

This multiparameter aspect of MR necessitates optimization of the imager for each combination of patient properties to achieve maximum clinical discrimination. To ensure optimal clinical use of MR imaging, some of the basic physics and engineering aspects need to be better understood and controlled.

The MR research program at the OCI can be separated into the clinical evaluation of a prototype 0.15T MR imager and a scientific investigation of the basic physics and engineering aspects of MR imaging.

Clinical Evaluation

Rigorous evaluation of new medical imaging modalities is difficult. We have structured our evaluation of the role of MRI in oncology in terms of the following questions (1):

1. Is the new technology used optimally?
2. How accurate is the information obtained?
3. How does the new modality compare with competitive modalities?
4. Does the new information impact ultimate medical outcome?
5. Is the medical impact worth the cost?

Answering these questions is a multi-step process which we have carried out in three specific studies: i) the detection of metastatic liver disease, ii) the spread of lung cancer into the mediastinum, and iii) extracapsular spread of prostatic carcinoma. Total accrual to the three protocols exceeds 400 patients and only preliminary results are presented here. The following table shows results for 91 patients comparing the accuracy of three modalities (MR, CT, and radionuclide imaging (RN)).

Comparison of MR, CT and RN in the Detection of Liver Metastases

	MR Positive		**MR Negative**	
	CT+	CT-	CT+	CT-
RN+	41	0	1	13
RN-	1	0	3	32

Total patients 91

Percentage agreement between MR and CT 96%
Percentage agreement between MR, CT and RN 80%

These results show that MR is essentially equivalent to CT in the detection of liver metastases. What remains to be done is to obtain truth data from biopsy, clinical follow-up and autopsy to arbitrate discrepancies among the three modalities. This will give a clearer evaluation of diagnostic accuracy but will be unlikely to change the conclusion that CT and MR perform equivalently.

Motion artifacts from breathing are the dominant limitation in the interpretation of hepatic MRI. Various techniques for suppressing these artifacts are being investigated which may improve the diagnostic utility of MR in this site. At the present time, because 3D acquisition is more susceptible to involuntary movement, the inversion spin echo technique is recommended.

The treatment of choice for primary lung cancer is surgical resection provided there is no spread of disease into the lymph nodes of the mediastinum. Spread of disease is usually assessed with mediastinoscopy or, if mediastinoscopy is negative, is sometimes discovered during attempted resection. We have studied how accurately MR can detect mediastinal nodal involvement and how it compares with CT in this aspect of lung cancer staging. Again, this is a region of the body where involuntary motion presents a problem. In this site, it is cardiac motion that limits image quality. Techniques for cardiac gating are well established for MR and have been used throughout our mediastinum study, either with 3D volume imaging or multi-slice imaging.

Our results indicate that MR and CT have almost identical performance in the detection of nodal involvement in lung cancer. ROC analysis on a series of 91 patients indicates that there is no statistically-significant difference in the performance of CT and MR for this site. These results are not surprising once we determined that MR is unable to distinguish diseased nodes from normal nodes on the basis of signal intensity. Thus, MR and CT both score involvement on the criterion of nodal enlargement. The somewhat increased contrast inherent in MR is fully offset by the better resolution of CT. Thus, in terms of staging of lung cancer, MR at the present level of development shows no significant advantage over CT.

Early reports indicated that MR could directly visualize prostatic carcinoma. Therefore, we studied a series of 54 patients with a distribution of normal volunteers, biopsy-proven carcinoma and benign prostatic hypertrophy (BPH) looking for contrast differences that would allow a differential diagnosis. No pulse sequence was found which would differentiate the three conditions. Direct measurements of relaxation times showed only insignificant differences among the three conditions.

However, in the course of these investigations we observed a bright rim around the normal prostate gland which was best visualized using a spin echo sequence with TE = 60 mS and TR = 2000 mS. An image depicting this rim is shown in Figure 1.

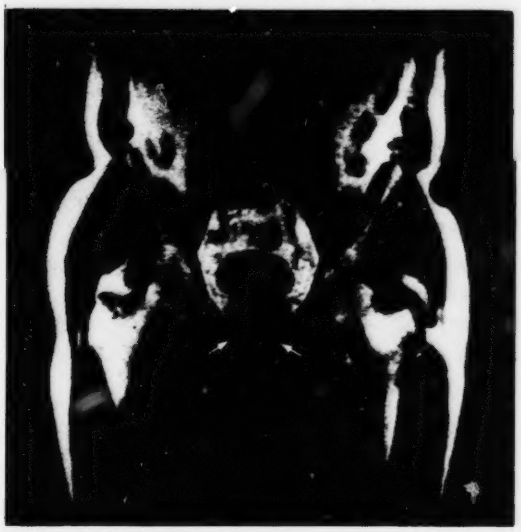

Figure 1. Coronal image of a normal prostate taken with a TE 60 mS and TR 2000 mS. Note the bright rim (arrows) around the prostate.

Although the rim has intensity similar to fat in this sequence, it can be shown in other sequences to differ from fat. We believe the rim is the periprostatic venous plexus (2).

In the case of prostatic cancer with known extracapsular spread, the bright rim is broken. Therefore, we have taken the continuity of the bright rim to indicate no extracapsular spread. A broken rim is indicative of extracapsular spread as is direct visualization of mass extending into the seminal vesicles. Using these criteria, the ability of MRI to stage prostatic cancer has been compared with conventional staging based on examination under general anesthesia (EUA) and cystoscopy. Preliminary results from 60 patients are tabulated below.

Extraglandular Spread of Prostatic Carcinoma

		EUA/Cystoscopy	
		Neg.	Pos.
MRI	Neg.	25	6
	Pos.	6	23

Percentage agreement $(25 + 23)/60 = 80\%$

Basic Science Of MR Imaging

MR images differ significantly from those of conventional imaging modalities because signal strength in the image has a complicated dependence on both the parameters of the tissues imaged, and the type of MR experiment performed to acquire the image. It is now clear that maximum tissue contrast in an MR image requires careful optimization of imager parameters for the body site, organ, and clinical application under investigation. Our work to date demonstrates our conviction that the basic physics and engineering aspects of MR imaging must be understood and controlled in order to ensure that optimum clinical information is obtained from MR images.

A number of fundamental factors have been investigated which contribute to the understanding and improvement of MR imaging techniques. Using special solenoidal coils, we have measured T_1 and T_2 relaxation rates *in vivo* in the mouse over the frequency range from 5 to 60 MHz. The T_1 contrast between normal and tumor-bearing legs was shown to decrease with increasing frequency, while T_2 contrast remained nearly constant. A comparison between *in vivo* and *in vitro* relaxation rates showed almost no difference. Significant increases in T_1 and especially T_2 were detected during the course of tumor growth before a palpable tumor mass could be felt (3).

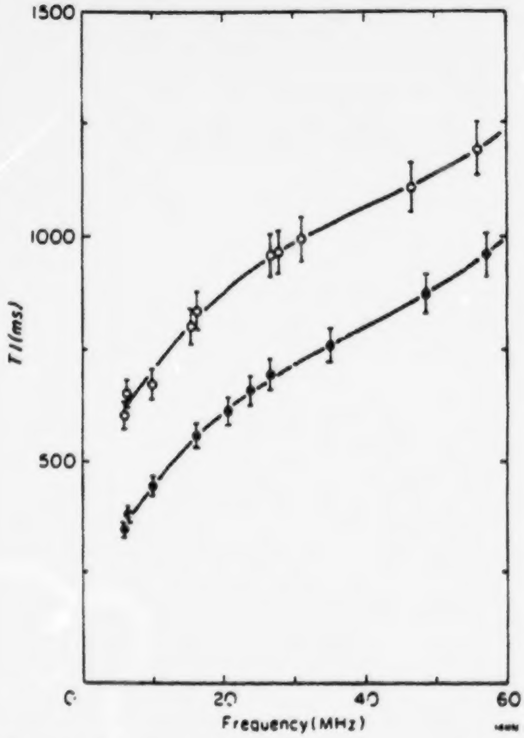

Figure 2. Variation of T_1 *in vivo* with frequency for normal mouse leg (closed circles) and tumor-bearing leg (open circles).

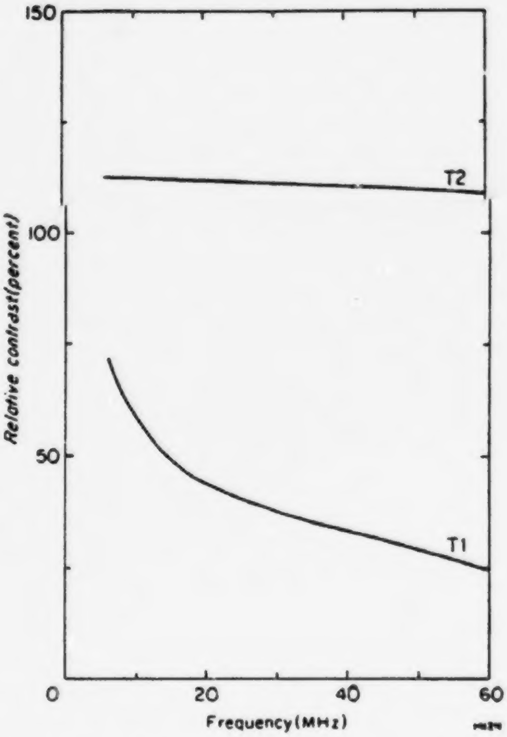

Figure 3. T_1 and T_2 contrast between tumor and normal leg versus frequency.

Radiofrequency (rf) absorption from 1 to 100 MHz was calculated for a cylindrical phantom and the accuracy of these calculations was verified by measurements at 25 MHz. For the range of dielectric properties likely to be encountered in tissues, there appears to be no fundamental limitation to MR imaging of the head up to 100 MHz, although phase shifts may present problems for inversion recovery techniques above 50 MHz (4).

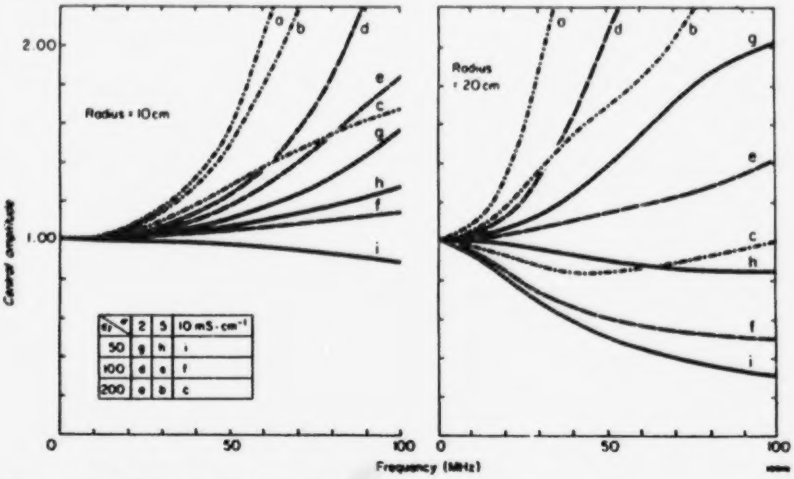

Figure 4. Calculated central amplitude of the rf wave in a 20 cm diameter phantom (left) and a 40 cm diameter phantom (right) as a function of frequency for various dielectric properties.

Basic physical aspects of MR imager performance were calculated and measured. Signal strength measured in MR images for various pulse sequences was shown to agree with calculations, and significant deviations which occurred for short repetition times or long echo times were explained. MR imager noise was measured and the effects of averaging, spatial filtering, temporal filtering and various sampling intervals were shown to agree with theoretical calculations. Motion artifacts were investigated and equations were derived which predict the amplitude and spacing of motion artifacts. A mathematical technique was developed which improves the edge-ringing artifact of MR images. Phantoms were developed which test MR imaging performance parameters and were used to quantify thermal streak artifacts.

These calculations and measurements of MR imager performance, and the understanding and reduction of imaging artifacts, are important contributions to the development and optimization of MRI.

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Nuclear Medicine

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The versatility of radionuclide techniques continues to promote the development of diagnostic procedures adaptable to a multitude of clinical questions; thus, the frontiers between research/development and clinical application are not always clearly defined.

During the past year we have been engaged in several projects to augment our capabilities for more informative investigation and accurate diagnosis using non-invasive means.

Lymphoscintigraphy

Studies in lymphoscintigraphy and evaluation of the technique continue. In collaboration with Dr. R.M. Clark, the clinical value of lymphoscintigraphy was assessed in 524 patients with breast carcinoma who underwent partial mastectomy, with or without axillary dissection. Results of the clinical correlation demonstrate a significant difference ($p<0.0005$) in actuarial survival between patients with a normal and those with an abnormal internal mammary lymphoscintigram. Increased mortality is associated with metastases to both internal mammary and axillary lymphatics, compared with involvement of either site alone, while the most favourable outcome is achieved by patients without involvement of either site. We have proposed that the current TNM staging for breast carcinoma henceforth include the status of internal mammary lymph nodes determined by radiocolloid lymphoscintigraphy (1).

Interstitial lymphoscintigraphy has recently been extended to examine the axillary lymphatics and we are currently evaluating the data to determine the diagnostic and prognostic features of this technique.

The reagent used in interstitial lymphoscintigraphy is critical for the quality of the study. Much of our earlier work was devoted to characterizing $^{99}\mathrm{Tc}^{m}$ antimony sulphide colloid as the reagent most suitable for an optimum image of lymphatics. Aware that different reagents may have unique advantages, we have evaluated other in this context. Recently we compared $^{99}\mathrm{Tc}^{m}$ antimony sulphide colloid and $^{99}\mathrm{Tc}^{m}$ dextran in rabbits and dogs. Despite the rapid dispersion of $^{99}\mathrm{Tc}^{m}$ dextran from the injection site and excellent delineation of the lymphatic vessels, lymph node uptake and sequestration was consistently lower than that obtained with $^{99}\mathrm{Tc}^{m}$ antimony sulphide colloid. $^{99}\mathrm{Tc}^{m}$ dextran, therefore, does not appear to be as well suited for distinguishing the features of lymph nodes as $^{99}\mathrm{Tc}^{m}$ antimony sulphide colloid (2).

Single Photon Emission Computerized Tomography

A significant technical advance in nuclear medicine has been the development of SPECT (single photon emission computerized tomography). The complexities of data acquisition, processing and image display are considerable and a careful appraisal of the circumstances under which this technique should be utilized in our institution is currently underway.

Radiopharmaceuticals

Besides technical innovations aimed at enhancing the means of data capture and display, developments in radiopharmaceuticals constitute the major avenues of breakthrough in recognizing and characterizing abnormalities and distinguishing benign from malignant processes. Potentially the most significant contribution in this area will come from the implementation of imaging with radiolabelled antibodies to tumor specific and tumor associated antigens. Presently in our radiopharmacy we are testing methods for radiolabelling immunoglobulins without impairing their biological properties. After refining these techniques we will apply them to labelling tumor specific antibodies.

All imaging modalities are complementary in recognizing different components of a pathological process. During the past year we have participated in a protocol comparing the relative accuracy of images of the liver obtained with x-ray computed tomography, (CT), magnetic resonance imaging, and radionuclides.

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Basic Studies Of Diagnostic Ultrasound

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The techniques used in medical ultrasonic imaging are closely parallel to the systems used for the underwater navigation technique called "Sonar". An ultrasound transmitter (transducer) is excited by a short voltage pulse, and generates a short burst of sound. This ultrasound pulse at general frequencies between 3 to 10 MHz propagates into the body at speeds of about 1500 M/sec. When this beam encounters various structures in the body, weak waves are scattered back to the receiver several seconds later (echoes). By scanning the beam across the body, a tomographic image can be obtained which displays the depth and strength of the echoes.

The ultrasound group are specializing in the design and development of special breast scanners, and the basic physical problems encountered in these systems. Ultrasound images from traditional scanners have a streaky appearance due to their poor lateral resolution (about 3 to 5 mm). We have developed a novel annular array/cone hybrid scanner which has a lateral resolution of only 0.5 mm (1). Based on this high-resolutional design, two breast scanners have been developed by the ultrasound group at are being evaluated at Princess Margaret Hospital and Women's College Hospital.

Many physics problems have been encountered in these systems, so detailed studies have been carried out to understand imaging and developing ways of improving their properties. These studies include a computer simulation of random scattering medium, and a theoretical and experimental analysis of the contrast and multiple scattering obtained from various transducer geometries. As well, an acoustic "macroscope" has been developed to study acoustic properties such as speed of sound, attenuation, and scattering amplitude for a thin samples of tissue.

Ultrasound Image Analysis and Improvement (Bly, Chahal, Kerr, Foster, Hunt)

Using various combinations of the annular array/conical transducer system, basic studies of scattering and beam properties in phantoms have been carried out to explain the limitations found in the acoustic images. In highly scattering phantoms, multiple scattering has been carefully documented (3) and the results indicate that such scattering may be important in some tissues such as the breast. A much more serious problem is artifactual signals found in echo-free volumes (i.e. cysts). A careful experimental and theoretical analysis of these structural signals has been carried out making use of various geometries of weak or strongly focussed transducers in the traditional pulse-echo modes, or in the combination of these apertures with the conical receiver. We have proven that these artifacts are closely related to the ensemble of signals produced from the beam components that are away from the observation point. Although the amplitude of individual scattered waves are extremely small, when are added in three dimensions, the values become important and greatly reduce the image contrast. The highly focussed, f/2.4 annular array transducer has demonstrated the best contrast in comparison to the poorer contrast of the high-resolution hybrid scanner.

One of the serious weaknesses of acoustic images is their streaky, speckled appearance. This is a fundamental problem of the acoustic waves, and is produced by interference patterns. Various techniques are being considered to reduce this speckle, and at the same time, to improve the detectability of features in the image. Various transducer geometries and image processing have been explored. The best arrangement is one in which a conical receiver is divided into eight sectors and the rectified signals are added together (phase insensitive sector addition) (5,6). Considerable improvement of the images was found in phantom and breast samples so that a practical scanning system is being developed.

Evaluation of Novel Ultrasound Scanners in Detection and Characterization of Breast Disease

(Fishell, Connor, Hunt, Foster, Blend)
This program is to evaluate the breast scanner and determine the potential of this system for the diagnosis of abnormalities. With the cooperation of Drs. Fishell and Connor, Women's College Hospital, over 950 patients have taken part in a trial and most have been examined for both ultrasonic and x-ray mammography.

Ultrasound is very successful in detecting and diagnosing benign abnormalities such as liquid-filled cysts and abscesses. In preliminary results, it appears that ultrasound is less accurate than x-ray mammography in detecting tumors, particularly for patients having fatty breasts. However, these two techniques complement each other since some carcinomas and cysts detected by ultrasound were not observed by x-ray mammography. As shown in Figure 1, a small carcinoma is clearly visualized by ultrasound, while serious dysplasia masks features displaying the x-ray mammography. A newer breast scanner is being evaluated by Dr. Blend at Princess Margaret Hospital. This system is more sensitive and has a much more rapid scanning rate. This program is continuing in a trial with the aim of determining the effectiveness of these breast scanners.

High-Resolutional Ultrasound Tissue Characterization (D'Astous and Foster)

A system called the "ultrasound macroscope" has been developed to measure the ultrasonic properties of tissues such as the breast (8,9). Based on the concept of a scanning acoustic macroscope, an ultrasound beam of frequencies from 3 to 13 MHz is focussed onto the sample, reflected by a speed of flat plate beneath it, and received by the same transducer. Speed of sound and scattering attenuation coefficient can then be calculated. The transducer is scanned in a slow raster motion so that images of these properties can be obtained and detailed analysis performed using a higher frequency design, high-resolution images (approximately 120 μm) of mammalian tissues are visualized. The results indicate that a combination of these parameters may have the best diagnostic potential. Figure 2 shows the macroscopic images from the same region of a thin sample of breast tissue containing a star-shaped infiltrating duct carcinoma. The images represent: a) backscatter; b) backscatter corrected for attenuation; c) attenuation and d) velocity. A 1cm diameter biopsy was taken in the centre of the tumor.

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X-Ray Imaging Research Program

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In the last decade we have witnessed an unprecedented growth in the development of new imaging systems in diagnostic radiology, such as CT, ultrasound, digital radiography, and magnetic resonance imaging. These techniques are revolutionizing diagnostic radiology as they provide information never before available. The development of new techniques as well as the improvement of existing techniques appears likely to continue. In all this work, the quest is to optimize the information content in the images or to present to the radiologist new information not available by other techniques.

This must be done with minimal risk to the patient, whether be it from x-radiation or other agents.

The main focus of our work is in developing improved methods of diagnostic imaging for the early detection of cancer. Our research is organized into the following projects:

1.0 Research and development of scanned projection digital radiographic imaging systems.
2.0 Application of dual energy techniques in order to obtain more quantitative information.
3.0 Collaborative projects with other groups in the physics division.
4.0 Development of devices for quality assurance in diagnostic imaging.

1.0 Scanned Projection Radiography (SPR)

1.1 Mammographic Imaging System (Yaffe, Fenster, Nishikawa)

In previous work (1,2,3) we have documented the limitations of conventional film imaging for detection of breast cancer. These limitations are related to the limited dynamic range of film, the inflexibility of the display contrast scale, the reduction of signal-to-noise radio due to structural granularity in the film and the dose efficiency of conventional mammographic film systems. We are developing a digital imaging system which promises to overcome these limitations. Preliminary images have been produced with this system and a detailed evaluation of the linearity and signal-to-noise properties of the system is being carried out so that it can be further optimized (Figure 1). Image quality is being evaluated by means of various objective test methods, by imaging standard phantoms and by imaging mastectomy and mammoplasty specimens and comparing these images to those produced on film with the help of radiologists specializing in mammography.

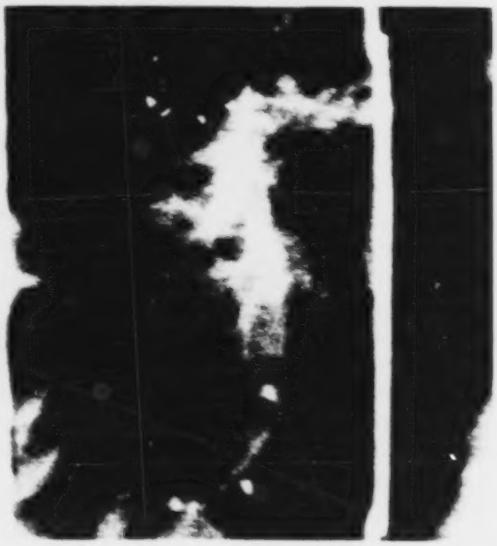

Figure 1. Experimental scanned projection digital image of excised breast tissue and calcified specks.

1.2 Xenon-Detector for Chest Radiography (Fenster, Cardinal)

We are developing (4,5,6,7) a new multi-element ionization detector for SPR chest imaging (Figure 2). This detector array has high spatial resolution, is dose efficient and is easy to construct. It consists of two plates separated by a 2 mm gap filled with xenon at 30 atm. One plate is the high voltage electrode and the other is etched to form an array of conductive strips (0.5 mm centre-to-centre) focussed on the x-ray source. Current work is aimed at increasing the resolution by about a factor of two. The detector with these modifications will be evaluated for chest radiography by imaging chest, contrast-detail and dual energy phantoms.

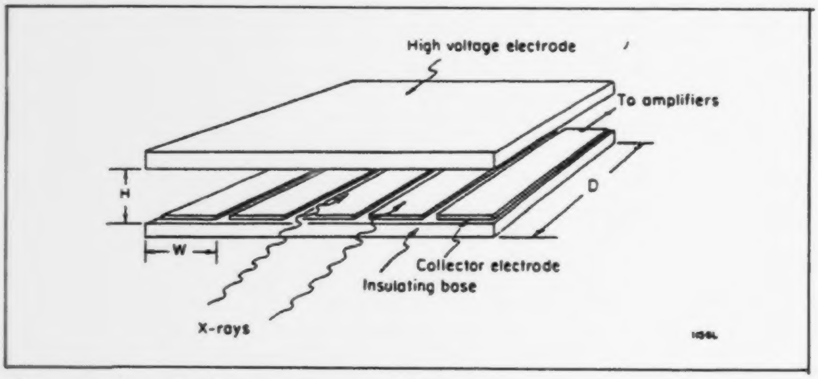

Figure 2. Schematic diagram of the xenon detector designed for scanned projection digital imaging.

2.0 Dual Energy Imaging

2.1 Chest Radiography (Fenster, Cardinal)

Detection of low contrast lesions using conventional radiographic systems suffers from high contrast obscuring shadows. These shadows are primarily caused by air/soft tissue or bone/soft tissue interfaces overlying the region of interest. Dual energy imaging allows the cancellation of a single material (such as bone) from the clinical image, and thus removes its obscuring shadow. The application of dual energy imaging is particularly promising in chest radiography, as it is possible to eliminate superimposed bone shadows.

Bone cancellation in chest radiography has been demonstrated by others using a dual-kVp technique in an SPR system. These systems scan the patient twice at different kVp's and obtain two images. Since SPR systems require a few seconds to produce a single image, the collection of two images would result in serious misregistration of the two images due to patient motion. A better method would make use of an energy-sensitive detector. Techniques for dual energy imaging in CT using an energy-sensitive xenon ionization detector were investigated in this laboratory a number of years ago. We are using the dual energy techniques already developed in our laboratory for CT (8,9) and our more recent developments in the design and construction of xenon detectors (4,5,6,7) for SPR imaging to develop an energy-sensitive detector (split detector) for SPR digital imaging.

2.2 Mammography (Yaffe, Johns)

It is possible that more information about the status of breast tissue can be revealed *in vivo* by performing energy-selective imaging of the breast. Different types of tissue have not only different x-ray attenuation at one energy but also different energy dependence of attenuation. This information can be exploited (10,11,12) to characterize tissues and produce hybrid images which may aid in diagnosis of disease. One example is an image in which the detection of microcalcifications (generally considered as a premalignant lesion) can be enhanced by appropriate manipulation of the dual energy images.

3.0 Collaborative Projects

3.1 Physical Characterization of Tissues ((Yaffe, Johns) with F.S. Foster (ultrasound group) and M.J. Bronskill, D. Brown (NMR group))

Researchers in the Physics Division are investigating imaging by several different modalities. In this study, which is a collaboration among the x-ray, ultrasound and NMR groups, breast tissue obtained from surgery and autopsy is evaluated on all three modalities in terms of the physical parameters which can be determined from each modality. From x-ray attenuation measurements the effective electron density and atomic number of tissue are determined over a range of energies. Ultrasonic attenuation and backscatter values as a function of frequency are measured on a specially-designed scanning device. Tissue samples are then analyzed in an NMR spectrometer to determine the T1 and T2 relaxation times versus frequency. Such information may be useful in characterizing the disease state, in optimizing imaging with each modality, and in deciding which may be the most useful in assessing different aspects of disease. Preliminary results suggest that two-parameter imaging may allow better discrimination between normal tissue and pathology.

3.2 High Energy Imaging for Therapy Verification (Fenster, Munro with J.R. Cunningham and A. Rawlinson (clinical physics group))

One of the major problems in radiation therapy is ensuring that the correct region of the body receives the x-ray treatment and that the surrounding tissues are spared. Therapy verification checks are used to visualize the regions of the patient exposed to the treatment beam. Film is currently used for therapy localization, however, film suffers from two problems: (1) the images obtained with film have low contrast so that anatomical structures are difficult to visualize and (2) use of film is labour intensive, requiring much time and effort to produce the (poor) images.

Two methods can be used to improve therapy localization: (1) modifying the treatment machines so that they can produce x-rays of diagnostic energies which are more suited to imaging or (2) developing an imaging device which can effectively use the high energy treatment beams to generate images. Modifying treatment machines would be quite difficult and would solve the localization problem for only those treatment machines that had been modified. An imaging device, however, would not only improve therapy localization on all treatment machines, but could be used for other tasks such as checking the x-ray beam being used to treat the patient (quality assurance checks) and checking the computer dose calculations used to predict the dose distribution within the patient.

A project has been initiated in collaboration with the radiotherapy group to develop an imaging device which can be used for therapy localization with high energy (6-25MV) x-ray beams. The project can be divided into two separate parts. First, various parameters of high energy x-ray beams will be measured (modulation transfer function, noise power spectrum) to determine what are the limits in image quality that can be expected when imaging with a therapy x-ray beam. Then a system will be designed (using this information) which can be used for therapy localization. Although the design details have not been finalized the imaging system will probably consist of the following components. The x-ray detector will consist of a tungsten plate which will efficiently interact with the high energy x-ray beams. The x-ray photons that interact will be converted into light photons by a fluorescent screen sitting in close contact with the tungsten plate. The image on the fluorescent screen will be reflected by a 45° mirror and focussed by a large aperture, high quality lens system into a vidicon tube capable of slow scan imaging. The lens, vidicon tube and any ancillary electronics will be outside of the primary treatment beam. The image will then be digitized, enhanced using image processing techniques and displayed on a TV monitor.

4.0 Anthropomorphic Radiological Phantoms (Yaffe, Caldwell)

The early radiologic diagnosis of disease depends critically on the optimization of image quality. Existing techniques for measuring image quality are useful but often must over-simplify the imaging task and do not provide a realistic test of the many aspects of image quality. We are developing a novel method for producing radiological test objects which closely simulate the x-ray transmission properties of the human body. The technique involves the extraction of information from actual patient radiographs using digital image processing methods and the incorporation of such detail into a test object by a combination of mechanical and photographic means. When such phantoms are radiographed they produce images similar to those from patients and facilitate the evaluation by radiologists of subtle differences in image quality.

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Immunology

Development And Specificity Of Cytoxic T Lymphocytes

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The T cell specificity repertoire (the sum total of all specificities carried by T cells) is strongly influenced by the environment in which it develops. Efforts of my group are focussed on trying to understand the nature of this influence and how it operates, particularly how T cells learn to distinguish self from non-self. T cells do not react with free antigen. They can only see antigen when it is presented to them on the surface of another cell. They recognize not only the (foreign) antigen but part of the (self) cell presenting it. They thus have a dual specificity for self and foreign. The self components recognized are cell surface glycoprotein molecules coded for within the major histocompatibility complex (MHC). An intriguing hypothesis is that the T cell repertoire develops through somatic mutation of cells which are initially reactive against self MHC products. There are two testable predictions of this hypothesis: (i) By looking in the right way, it should be possible to detect large numbers of T cells reactive against self MHC; (ii) There must be a special mechanism for controlling these self reactive cells. We currently have data supporting both these predictions.

Large numbers of cells reactive against self MHC products can be obtained from limiting dilution microcultures of athymic nude bone marrow (1). Similar results have recently been obtained from normal bone marrow (Benveniste, unpublished). Current studies are consistent with the hypothesis that these autoreactive cells represent an early obligatory step in repertoire development: cultures with autoreactivity later develop alloreactivity and modified-self reactivity (Benveniste, unpublished).

Specificity continues to evolve rapidly during an ongoing immune response. In several different types of mixed lymphocyte reaction, we have shown that a single T cell clone can contain more than one specificity and that the specificities within a single clone can change in time with the direction of change being influenced by the environment in which the T cells develop (2). Currently we are trying to look for expression of and changes in the genes coding for the T cell receptor in these rapidly changing clones.

Over the last five years, we have established the existence of what appears to be a new class of regulatory cell ("veto cells") whose role appears to be the control of autoreactive cells (3) and have made substantial progress in determining their mode of action (4). Up until recently, we had thought of the role of the veto cell as being limited to T cell ontogeny. However, current results suggest that veto cells may play an important role in an ongoing immune response. We have been studying long term cytotoxic T lymphocyte (CTL) lines maintained in vitro. These can only be maintained by continuously providing both growth factor and stimulator cells. To our surprise, we found that CTL lines possess high levels of veto activity against T cells capable of recognizing the MHC of the CTL line (5). When the CTL line is cultured without stimulator cells, it rapidly becomes self reactive (6). These results imply that T cell specificity is not stable but is maintained by the environment in which the T cells develop. We are currently inyestigating in more detail the relationship between veto activity and self reactivity in these CTL lines. Speculations on the nature of the structures being recognized by auto-reactive T cells led to the hypothesis that cell surface sugars may be involved. We have shown that glycopeptide extracts from three MHC-different tumor cell lines can specifically inhibit allogenic T cell recognition in an MHC-restricted manner (7 and unpublished). These results imply that cell surface glycosylation is somehow under the control of MHC and that the T cell receptor complex has lectin-like properties. We are currently analyzing glycopeptide preparations from MHC-transfected cell lines.

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Immunoregulation In Infectious Disease And Tissue Transplantation

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The body's immune system plays an important role in the normal defense against infectious diseases. Major advances in clinical medicine in the earlier parts of the century came from the ability to vaccinate individuals for protection against eg. poliomyelitis virus, smallpox etc. There are still however a number of parasitic diseases, endemic in Third World countries, which cause enormous clinical and socio-economic problems. The World Health Organization has listed six of these diseases as being of vital importance to contain/eradicate in a move towards greater global health. We are probably all familiar with the first on the list (malaria). One of our lab's efforts is designed towards developing a vaccination strategy for another of these diseases, cutaneous leishmaniasis.

In some instances we are more concerned with "down-regulation" immunity rather than with enhancing an immune response (as in vaccination). One such instance is when a foreign tissue is grafted (for medical reasons) onto a recipient. Our lab has invested considerable time in the analysis of this rejection process, and the means by which it can be controlled.

We have most of us been exposed at some stage to comments of the type: "Cheer up (emotionally) or you'll get sick (physically)." There are now a number of reports which claim to show that the immune system itself is an interceding agent in this interaction between psychological behaviour and health/disease. We are exploring this possibility from two angles: (i) does psychic stress (eg. tax accountants at the end of the fiscal year; medical residents prior to fellowship exams) affect immune-response parameters? and (ii) does sleep affect immune functions?

Regulation Of Immune Response To *Leishmania* Infection (Gorczynski, Rogers, Boulanger)
BALB/c mice infected with the human intracellular pathogen *L. braziliensis* develop a non-healing cutaneous lesion which eventually metastasizes viscerally and causes death. Animals can be protected by vaccination with attenuated forms of the parasite. Vaccinated mice develop immune cells capable of transferring protection to naive animals. We have prepared a number of monoclonal antibodies against these avirulent parasites and are attempting to define the relevant antigens necessary to produce immunity to parental parasites. In addition, we are exploring the possibility of (i) using anti-antibodies as a form of antigen-mimicry to produce protection, and (ii) using DNA transfer techniques to define the defect(s) in BALB/c macrophages which allow for relatively uncontrolled parasite proliferation.

Tolerance To Tissue Allografts (Gorczynski, Rogers, Boulanger, Gontovnick)
Neonatal exposure of mice (A) to cells of mice (B) inhibits the normal ability of adult mice (A) to reject grafts from B. A is now said to be tolerant of B. The mechanism for this tolerance state is unclear. However, we have reported at length in the past, evidence consistent with active suppression of potentially reactive (A anti B) cells rather than deletion (i.e. loss) of the same, as being of crucial importance. Since the major cells responsible for A anti B activity are so-called T lymphocytes the problem also becomes one of assessing where and how T cell differentiation and antigen-reactivity are established. Recent and new evidence suggests that there is a thymus-dependent and a thymus independent stage of development of antigen reactivity in T cells. Moreover, brief (24 hr) exposure of thymus cells of tolerant mice to standard tissue culture conditions seems to result in a total loss of specific suppression.

Immune Regulation By Other Physiological Systems (Gorczynski, Mowat, Stanley, Keystone, Dorian, Muldovsky, Lue)
We and a number of other groups have established that under stress, a variety of parameters of immunological responsiveness seem to decline. We followed a group of accountants and a group of psychiatry residents for a 2-year period and asked whether there were predictable changes in immune functioning associated with changes in psychological state (assessed by a number of self-administered questionnaires). The most dramatic changes seen were in terms of a decline in a natural killer (NK) cell level/activity and in interleukin production with stress. NK cells are believed to be of importance in overall immunoregulation, and have been implicated in surveillance against tumor cells. Interleukins are molecules used by cells in the immune system to 'talk with', and regulate the function of, other immune cells. We have no evidence yet that intervention to reduce stress can alter these changes.

Why do we sleep? Does sleep have a restorative value on a key body function(s)? We again followed a number of immunological parameters in eight volunteers over a period of 24 hours and assessed also their mood states (sleep) by conventional criteria (EEG etc.). Onset of slow-wave-sleep was strongly correlated (P 0.001) with a burst of release of interleukin-1 and a decline in NK levels/activity. We are currently exploring the source of IL measured, and also the likelihood (using sleep deprivation studies) that these immune functions are related to sleep-state and not a circadian rhythms per se. The modification of immune function during sleep becomes an important problem to address in light of other studies showing changes in immune function with disease. Are these changes epi-phenomena of altered sleep behavior?

Mechanisms Involved In T-Cell And B-Cell Interaction

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Our laboratory is interested in molecular mechanisms involved in T cell- B cell (T-B) interaction. For this study, it is essential to establish monoclonal B cell lines expressing surface IgM receptor molecules for defined hapten specificity. To this end, we have constructed several B lymphoma lines carrying surface IgM specific for hapten, TNP by transfection of cloned antibody genes specific for TNP into the B cell lines. Some of the transformants were shown to proliferate responding to antigen specific stimulation. This system is extremely useful for analyzing biochemical changes in B cell activation.

T-B interaction is regulated by MHC restriction. We have constructed vectors carrying $IA\alpha^k$ and $IA\beta^k$ genes. B lymphoma lines ($H\text{-}2^d$) transfected with the vector were shown to express $IaA\alpha^k A\beta^k$. We have been working on ontogeny of children's leukemia. Gene rearrangement (antibody genes and T cell receptor genes) were demonstrated to be a good tool to study ontogeny of leukemic cells.

About 30% of non T- non B leukemia carrying antibody gene rearrangement were shown to carry T cell receptor *β*gene rearrangement suggesting heterogeneity of non T- non B leukemia.

One of the most fundamental approaches is to establish inducible transformation system. To this end, we have constructed metallothionein promotor driven activated oncogene Ha-ras, designated pMTEJ. When introduced with non-malignant rodent cells, the vector permits inducible cellular transformation controlled by heavy metals.

Currently we are studying biochemical changes in malignant cells.

T-cell Antigen Receptor

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The immune system provides protection against infection from the environment, in both a specific and non-specific manner. In addition, the immune system may play a role in protecting against the early stages of malignancy. The specific immune system consists of humoral and a cell-mediated mechanism. In either system, a protein molecule is produced which can specifically recognize a foreign antigen. As there are a very large number of foreign antigens, the immune system must have a way of producing an equally large number of receptor molecules.

In addition to the immune system being able to recognize foreign antigens, it must also be capable of recognizing and avoiding self-antigens; failure to control this aspect of the immune response may result in development of auto-immune diseases such as rheumatoid arthritis, systemic lupus erythrematosis. The humoral immune response is the main protection against bacterial infections. The cells involved in this response are the B-lymphocytes which carry immunoglobulins on their cell surfaces as antigen receptor molecules.

Antigen recognition for the cell mediated response is known to be mediated by T-lymphocytes; however, until recently, the molecular mechanism underlying T-cell recognition eluded investigation. In the past year, we and others have isolated genetic information for the *α*- and *β*-chain of the cell receptor on T-lymphocytes (T-cell receptor, TcR). Molecular analysis indicate that *α*- and *β*-chain of the TcR are distinct genes from immunoglobulin being only partially homologous to Igs. Furthermore, the genes coding for these proteins are situated at different locations of the human and mouse chromosomes. The organization of these genes, however, is similar to those of Ig genes being composed of non-contiguous segments of variable, joining, and constant region segments. In addition, diversity gene segments are also present, and are used in most, but not all, *β*-chain and possibly *α*-chain messages. Furthermore, short recognition sequences adjacent to these elements thought to be involved in recombination process, were also found. Using gene transfer technology, we have also been able to reconstitute a biologically active T-cell receptor. This finding provides direct support for the hypothesis that the *α*-*β* heterodimer encodes the T-cell antigen receptor. This will provide a basis for further examination of the T-cell antigen receptor as a recognition and signal transduction molecular complex.

With the use of the T-cell receptor genes, we have also examined cells from hemopoiesis malignancies and allied disorders for rearrangement of these genes. These studies will help in the diagnosis and maintenance of patients with T-cell malignancies and lymphocytosis.

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Medical and Radiation Oncology

Antibiotic Studies

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Physicians at The Princess Margaret Hospital have been involved in multi-centre national trials on new antimicrobial agents as they become available for clinical evaluation. In many of these studies, Dr. Feld is the coordinator in his role as Chairman of the Clinical Trials Committee of the Canadian Infectious Disease Society and Chairman of the Infection Subcommittee of the National Cancer Institute of Canada (NCIC). This has led to The Princess

Margaret Hospital being involved in trials specifically designed for the neutropenic cancer patients and those designed for patients with or without malignant disease. In addition to the information about new agents, these trials provide the best available patient care for hospitalized patients with infection.

1. IC4

We have been entering patients on the NCIC trial in febrile neutropenic patients (IC.4) comparing azthreonam plus cloxacillin to tobramycin plus athreonam versus a control arm of tobramycin plus moxalactam. The study has just been discontinued as it was found that the tobramycin plus moxalactam (the control arm) was superior to either of the other two arms with no major toxicity differences.

2. A study comparing trimethoprim-sulfamethoxazole to ciprofloxacin in uncomplicated urinary tract infections is continuing to accrue patients. This is a multi-center double-bind trials. The study agent (ciprofloxacin) is a new oxyquinilone derivitive related to nalidixic acid that covers most of the common urinary tract pathogens but in addition, is active against pseudomonas. This agent is being studied in an oral form but a parenteral form is also presently being evaluated.

3. We are entering patients on a double-blind randomized trial comparing a single dose of a long-acting third generation cephalosporin, ceftriaxone to four doses of a standard shorter half-life third generation cephalosporin, cefotaxime. If the study drug turns out to have at least equivalent activity, an agent that can be given once a day possibly as on an out-patient basis will be available to the physician for serious infections.

Bone Marrow Transplant Program

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The Bone Marrow Transplant Program at The Ontario Cancer Institute provides a basis for integrated clinical and laboratory research. We have concentrated our efforts to evaluate the effect of standardized preparative protocols and to develop new prognostic parameters for the clinical outcome based on bone marrow cell culture studies.

Since 1979 the patients have been prepared with standardized regimens. Patients with chronic myeloid leukemia (CML) and acute myeloid leukemia (AML) receive cytosine arabinoside (100 mgs/kg/dayx5), cyclophosphamide (60 mgs/kg/dayx2) and 500 cGy total body irradiation (TBI) at 50 to 85 cGy per minute. Patients with acute lymphoid leukemia (all) are treated with vincristine (2mgs), prednisone (200 mgs/dayx5), L-asparaginase (30,000 units/dayx5), cyclophosphamide (16 mgs/kg/dayx2) and TBI at 500 cGy. The dose and dose rate of TBI is unique to the program at the OCI. The overall disease free survival of 108 patients transplanted with acute and chronic leukemia (25 ALL, 35 AML, 48 CML) was 55% with median follow-up of 28 months. The disease status at the time of transplantation represented a major risk factor. Patients with acute leukemia in first remission or stable chronic phase CML showed a 65% survival with a relapse rate of 7%. In contrast, patients transplanted with more advanced disease had substantially lower survival with a relapse rate of 35%. In addition to disease recurrence, the main life-threatening complications following the bone marrow transplantation were associated with severe GvHD and viral infections, particularly related to cytomegalo virus (CMV).

Initiatives were launched in three major areas to improve the clinical service, to advance knowledge about hemopoietic reconstitution after bone marrow transplantation and to evaluate clinical and research data with a computerized record system. Three clinical studies were initiated to deal with these.

A clinical pilot study is near to completion using Cyclosporine A therapeutically for established severe GvHD. The data are encouraging as indicated by an increase in the proportion of patients surviving the first three months post-transplantation from 70% to 85%.

The problem of viral infections is currently addressed with a double blind randomized study to evaluate the prophylactic use of Acyclovir. An alternative protocol was developed to prepare high risk patients with cytosine arabinoside, VP16 and TBI. It is too early to evaluate the efficacy of this approach.

Laboratory efforts to examine the role of clonogenic hemopoietic precursors in bone marrow transplantation. The frequency of pluripotent and single lineage clonogenic hemopoietic precursors within the transplant inoculum and in the recipient prior to and post engraftment were analysed to determine whether they may serve as attributes predictive of clinical outcome. The total number of nucleated cells in the transplant inoculum was found to be a strong predictor of survival. Clonogenic cells were not predictive of the time to engraftment or survival. Longitudinal studies of transplant recipients demonstrated that the frequency of clonogenic cells does not return to the normal range in spite of their ability to maintain normal blood counts. In contrast to normal hemopoiesis, almost all pluripotent precursors participate actively in the cell cycle indicating a marginal reserve.

Based on the analysis we have begun to transplant patients with more than 2.5 per 10^{10} nucleated cells whenever possible. The increased cell load has resulted in a more complete engraftment as determined by the frequency of clonogenic precursors in the recipient.

The development of a prospective computerized record keeping system has now reached its clinical application. This tool will allow rapid analysis of clinical trials and laboratory studies associated with the bone marrow transplant program.

Breast Cancer

Members of the Breast Group

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During the past year, more than 1,200 new patients with breast cancer and 18,181 follow ups have been seen by this Group. In addition, 115 new patients and 396 follow ups were seen in the Breast Diagnostic Clinic. These numbers are increasing with the advent of new studies.

We are actively involved in studies assessing the value of adjuvant hormone and chemotherapy and also conservative treatment.

Our Institute has pioneered the concept of breast conservation since it opened in 1958. This method of treatment has been gathering momentum in recent years resulting in the referral of many more patients with early breast cancer who previously would not have been referred to this Hospital. These patients are treated surgically by partial mastectomy ("lumpectomy") and axillary dissection.

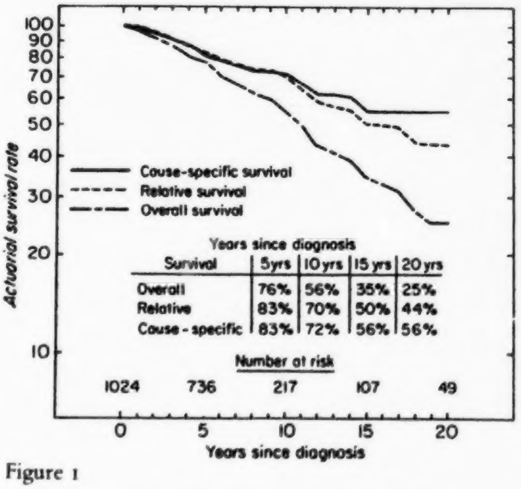
It is now accepted that irradiation of the regional nodes may reduce local recurrence but does not improve survival. The trend is now to irradiation only to the breast after partial mastectomy and axillary dissection, or in some instances, careful follow up with no radiation. Many patients are also referred for palliative treatment after the development of metastatic disease. Hormone and chemotherapy studies are also available for these patients. Palliative irradiation of metastatic disease forms a large component of the work in the Department of Radiation Oncology. As breast cancer is a very common disease, the work load is heavy and exacting. It is also a capricious disease and patients may live for many useful years even in the presence of active disease. This, therefore, creates a very large number of patients requiring continual long term follow-up.

Separate working groups have been developed in the Departments of Medicine and Radiation Oncology and the two groups meet frequently to discuss the progress of studies and plan future treatment policies. Studies are carried out in co-operation with the Toronto Breast Group and the new Ontario Clinical Oncology Group in association with University teaching hospitals.

Patients are followed not only at The Princess Margaret Hospital but also in all the peripheral clinics. The group is assisted by the following clinical trials nurse: B. Sinclair-Murray, M. Clarke, C. Mayers, T. Baskerville.

Conservation Therapy — Retrospective Study
From January 1958 to December 1980, we accumulated a total of 1,024 patients who were treated by partial mastectomy prior to referral to The Princess Margaret Hospital. None of the patients included in this study had clinical evidence of regional nodal involvement. Following partial mastectomy, most of the earlier patients received post-operative irradiation to the breast and regional nodes but, more recently, 263 patients were treated by excision only, with no irradiation and 327 received radiation therapy only to the breast. Patients were excluded from analysis if adjuvant therapy had been given, to avoid bias.

The overall actuarial survival of this group at five years was 76% and at ten years 50%. The relative survivals were 83% and 70% respectively. (Figure 1).



Years since diagnosis

Survival	5yrs	10 yrs	15 yrs	20 yrs
Overall	76%	56%	35%	25%
Relative	83%	70%	50%	44%
Cause - specific	83%	72%	56%	56%

Figure 1

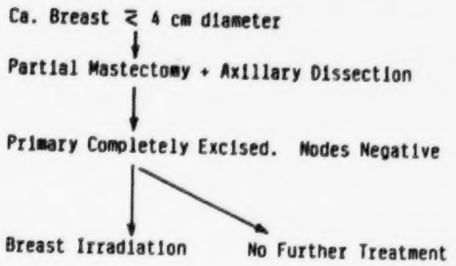
There was no difference in survival whether radiation was given or not. Patients treated by partial mastectomy with no other treatment had the same survival at ten years as those who were irradiated. The breast relapse rate was undoubtedly higher in the unirradiated group but this did not appear to be detrimental to survival.

The survival of this group of patients therefore compares favourably with reported survival rates for radical surgery.

Conservation Therapy — Prospective Study
As a result of the retrospective study, we have

commenced an Ontario-wide prospective study as outlined here:

Ontario Clinical Oncology Group Study


Ca. Breast ≲ 4 cm diameter
Partial Mastectomy + Axillary Dissection
Primary Completely Excised. Nodes Negative
Breast Irradiation
No Further Treatment

With strict surgical radiotherapeutic and pathological control, we hope to be able to define more accurately those patients whom may or may not require post-operative irradiation. Dr. R.M. Clark (OCI) and Dr. P.B.M. McCulloch (OCTRF) are co-principal investigators and the study is supported by the new Ontario Clinical Oncology Group (OCOG). Centres participating in the study are: Ontario Cancer Institute, Ottawa General, Ottawa Civic, Hamilton and Thunder Bay.

In the first year of this study, 150 patients have been randomized.

Two-Dose CMF Study

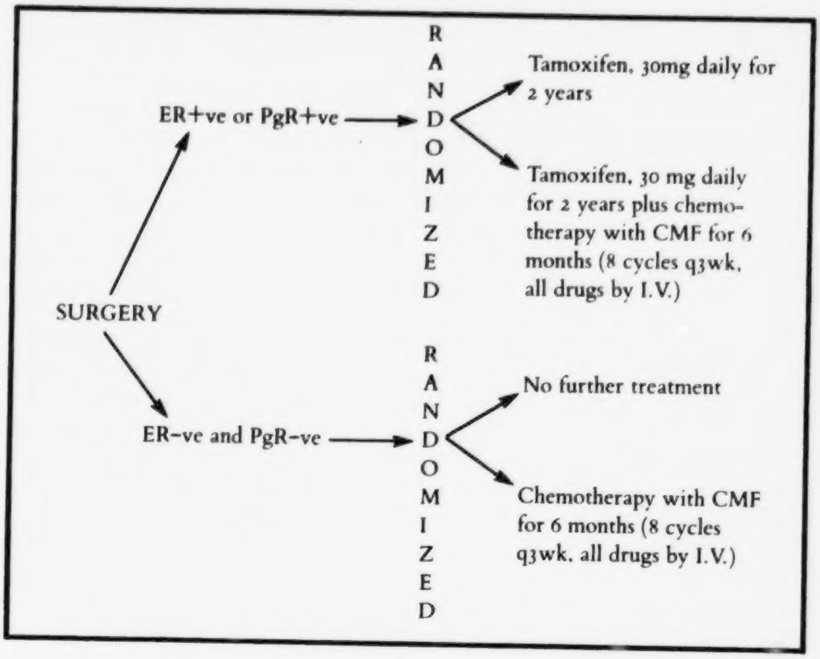
A study is being undertaken in patients with metastatic breast cancer who are about to receive their initial chemotherapy for advanced disease. Patients are asked if they would consent to be randomized between treatment with conventional full-dose chemotherapy using cyclophosphamide, methotrexate, and 5-fluorouracil, or to initial treatment with half-dose chemotherapy. Patients are followed for response to treatment, the quality of their life while receiving chemotherapy using linear analogue self-assessment, and for survival.

This study seeks to enquire whether optimal palliation is achieved with full-dose chemotherapy (thereby increasing the potential for side-effects), or whether it may be achieved with lower doses with the possibility of fewer side effects. More than 100 patients have now been entered into this study and accrual of patients continues.

A Study Of Adjuvant Therapy In Post-Menopausal Patients With Node Positive Breast Cancer

In the spring of 1984, a trial of adjuvant therapy in patients with node positive breast cancer was commenced with the collaboration of the Princess Margaret Hospital, the University of Toronto Teaching Hospitals and the Cross Cancer Centre in Edmonton, Alberta. The study format is outlined in the following schema:

A Trial Of Adjuvant Post-Surgical Treatment Of Breast Carcinoma In Post-Menopausal Patients With Histologically Involved Axillary Nodes


SURGERY
ER+ve or PgR+ve
RANDOMIZED
Tamoxifen, 30mg daily for 2 years
Tamoxifen, 30 mg daily for 2 years plus chemotherapy with CMF for 6 months (8 cycles q3wk, all drugs by I.V.)
ER−ve and PgR−ve
RANDOMIZED
No further treatment
Chemotherapy with CMF for 6 months (8 cycles q3wk, all drugs by I.V.)

The study is designed to answer two questions: 1) the role of combined chemotherapy and hormonal treatment in node postive/receptor positive patients as compared to hormonal treatment alone, and 2) to evaluate the role of chemotherapy in node positive/receptor negative patients as compared to no further treatment. The rationale for this study is based on a previous trial comparing tamoxifen to no therapy in estrogen receptor positive patients, in which an improvement in disease-free survival was seen in patients receiving adjuvant tamoxifen. This study has been reported on in abstract form (N407 ASCO Proc. 1983) and further analysis of data has been submitted and will be reported at ASCO this year. In node positive receptor patients an effective adjuvant progress remains to be established, thus we felt justified in studying chemotherapy versus no treatment in this group of patients.

Beginning in the fall of 1984, the NCI entered into a collaboration with the original study participants and this trial is currently being carried out across Canada under the designation of MA-4. Approximately 300 eligible patients are required and accrual on the trial has been excellent. Currently 102 patients have been entered cross-Canada, with 52 from the Toronto-Edmonton investigators. This study is on-target and should finish accrual within the 4-year time frame initially established.

Prospective Randomized Controlled Trial of Adjuvant Tamoxifen in Postmenopausal Women With Axillary Node Positive Breast Cancer

Postmenopausal women with axillary node positive breast cancer were randomized to receive either tamoxifen 10mg t.i.d. for 2 years or no further therapy after modified radical mastectomy plus regional radiotherapy consisting of 4,000 rads to the supraclavicular nodes and both internal mammary node chains (radiation subseries). Stratification included tumor size, nodal status (1-3 +ve vs. >4 +ve), and time since menopause. Three hundred and six women (195 in the main series and 111 in the radiation subseries) had a median follow-up of 2.6 years. Overall three year actuarial relapse free rates were 62% for the tamoxifen treated group vs. 49% for the control group (p=.087) Wilcoxan Gehan test). In the main series, three year relapse free rates were 70% for those treated with tamoxifen vs. 57% for controls (p=.039) while in the radiation subseries they were 49% for tamoxifen treated patients vs. 38% for controls (p=.867). There was no difference in overall survival for the entire group or for either subseries. Estrogen receptor status was known inn 195 patients and progesterone receptor status in 186. The improvement in disease free survival seen in the main series appeared to be confined to the receptor positive sub-group. Our early results suggest that tamoxifen is useful in decreasing recurrences in postmenopausal women with axillary node positive breast cancer following mastectomy. This benefit appears to be confined to women with receptor positive breast cancer who have not received postoperative radiation therapy.

As of May 1st, 1985, 61 patients have been entered on study - 38 from Toronto and 23 from Calgary. The target accrual is 130 patients. This study is accruing at the expected rate and entry should be completed within a year.

Randomized Cross-Over Comparison of Mitoxantrone and Adriamycin in Patients With Advanced Breast Cancer

Although chemotherapy provides palliation and prolongation of life in selected patients with breast cancer, its use has been tempered by adverse effects such as vomiting, hair loss and cardiotoxicity. In recent years an effort has been made to synthesize drugs with potency equivalent to conventional agents but reduced toxicity. One of these new drugs, mitoxantrone, is being tested as an alternative to adriamycin, the most active antineoplastic agent currently available for the treatment of breast cancer. Initial experience suggests that mitoxantrone is very well tolerated, but its efficacy and extent of crossresistance with other agents are uncertain.

A randomized trial of mitoxantrone versus adriamycin has been initiated for patients with metastatic breast cancer who have previously been treated with cyclophosphamide, methotrexate and 5 fluorouracil (CMF). The study objectives are: l) to compare response rates for the two drugs as second line therapy; 2) to compare their toxicities and effects upon quality of life and; 3) to determine, by cross-over to the other drug at the time of treatment failure, the degree of cross-resistance between these two drugs. Two hundred and twenty patients will be accrued. The trial started in early l985 and results are not currently available.

If mitoxantrone demonstrates less toxicity than adriamycin and is equally effective it will replace adriamycin as the cytotoxic drug of choice for breast cancer patients who have relapsed/progressed after CMF.

Data Management System For Acute Leukemia And Bone Marrow Transplant Programs

J.E. Curtis, M.D., Medical Oncologist

During the past year, work has been begun on the establishment of a Data Management System for the Acute Leukemia and Bone Marrow Transplant Programs at The Ontario Cancer Institute incorporating The Princess Margaret Hospital (OCI/PMH). Recent clinical studies in acute myeloblastic leukemia (AML) at OCI/PMH have shown that improved clinical results and new research objectives are possible through the close integration of laboratory research and clinical observation. The studies reported elsewhere in this report (See "The Blast Cells of Acute Myeloblastic Leukemia" and "Acute Leukemia — Results of Clinical Trials") have demonstrated the role of biological properties of leukemic cells in determining the outcome of patients with acute leukemia, and the usefulness of laboratory research in planning treatment strategy.

The Bone Marrow Transplant Program has been developed to make this important treatment modality available to our patients with acute and chronic leukemia. Marrow transplant offers a radical new form of treatment with the potential for cure. It is, however, a procedure associated with considerable morbidity and mortality. The research program in bone marrow transplantation is not as developed as laboratory research in acute leukemia. Because of the developmental nature of bone marrow transplant, careful analysis of clinical results and the development of new treatment strategy is essential for an up-to-date program.

Crucial to the development of the Data Management System has been the employment of a Data Manager. A Data Manager is essential for coordinating the design of the system, developing methods of data collection, designing the appropriate forms for data collection, supervision of entry of data into the computer, assisting in analysis of data collected, and protocol management and planning. This individual provides the link between the computer expert, the statistician, the research scientists and clinician.

Utilizing existing hardware,and as much as possible, existing software through the Computer Services Department of the OCI/PMH, a Data Management System has been set up. This is now beginning to function for both the Acute Leukemia and the bone Marrow Transplant Service. Clinical data are entered into the computer as soon as it is obtained. The data are in a form that can be retrieved by the clinician or by an investigator at various terminals throughout the OCI/PMH. In the near future data will be summarized in a form which will be suitable for inclusion in the hospital record. This is not expected to be a substitute for the traditional hospital record, but to provide additional information in a form that is more suitable for the ongoing management of patients.

In conclusion, a Data Management System at the OCI/PMH has been established for both the Acute Leukemia and Bone Marrow Transplant Programs. This system is beginning to function and is already being used for protocol management, for individual patient management and for the correlation of research information with clinical outcome.

Dermatologic Oncology

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Carcinomas of the skin are the commonest of all cancers. Most occur on the head and neck. They are disfiguring but less than 1% of patients have a tumor related death. The cancers can be managed in a variety of ways. The OCI/PMH clinic is multidisciplinary and most new patients together with all problem cases are reviewed at a weekly conference. Because of the increased numbers of other specialties that treat skin cancer, the number of new cases seen annually has fallen to just over 600. However, 25% of patients develop a second cancer within one year and overall about three-quarters of patients develop multiple tumors. These repeat patients account for a significant portion of the workload. The clinic also acts as a tertiary referral centre for the province. A number of patients are referred for a second opinion because of the extent, complexity or rarity of their tumor. It is only by concentrating the experience with rare lesions in one clinic that the natural history of the tumor and eventually optimum treatment can be determined.

New patients are worked-up by the resident staff and presented to the staff physicians at a weekly working conference. This also serves as a teaching forum where problem and interesting cases are also reviewed. Because of the accumulated numbers of follow up patients a well-skin clinic has been established to review patients on a long term follow-up. However, many elderly out-of-town patients are discharged to the care of their family physician after three years. Each month there is a major skin conference attended by other dermatologists, surgeons and residents in the University of Toronto Dermatology Program. It has become a valuable part of their core teaching and has fostered excellent relationships with physicians who refer patients to our clinics.

The dermatology section of the Skin Clinic sees approximately 500 patients a year. Of this number about 50% are new referrals and consultations. The new cases divide just about equally between patients having problems with sun damaged skin and skin carcinoma, most of whom require treatment and those that have purely dermatologic problems incidental to their primary disease. Approximately 75% of all patients require some procedure such as a biopsy, cryotherapy, electrodesiccation and curettage or intralesional therapy. The surgical section specializes in the surgical treatment of skin cancers and especially those that recur following radiotherapy. Many patients are referred specifically to the hospital for radiotherapy and this accounts for it being the major treatment modality.

During the past year there have been several clinical reviews. This clinical research is specifically aimed at finding optimum treatment for tumors at different sites but is also of value in quality control.

Skin Cancer of the Head and Neck

A review of 498 patients with 584 skin cancers occurring on the head and neck and seen between 1971 and 1976 was reported.(1) There were 433 basal cell and 151 squamous cell carcinomas for a ratio of 1.9:1. The media age for developing skin cancer was 69 (22-92) years and there was a male to female advantage of approximately 1.5:1. All of these tumors were treated by radiotherapy with the primary tumors being controlled at three years in 533 instances (94.7%). None of the basal cell carcinomas metastasized. Cervical node metastases developed in 12 patient (8%) with squamous cell carcinoma. Overall there were four (0.8%) tumor related deaths.

Acute Epithelioma

An aggressive squamous cell carcinoma of the skin has been identified for which we have suggested the name acute epithelioma. It is frequently larger than 2 cm and has a characteristic morphology with raised, rolled, vascular, but not everted edges. Commonly there is a central crust covering a foul discharge on papilliferous base. Biopsy is characteristically ambiguous but often that of a cell differentiated squamous cell carcinoma. Irrespective of the history, which is usually short, all tumors have a period of rapid growth. Among 193 patients with squamous cell carcinomas of the eyelids or external ear 24 (14%) were designated as being acute epitheliomas. The main differences between the typical squamous cell carcinomas and acute epithelioma are summarized in Figure 1. Fortunately the primary tumor was controlled for both groups in 95% patients. However the three-year-cause-specific survival rate was 95% for the typical tumors compared to 80% of the acute epitheliomas. It is postulated that these acute epitheliomas are virus induced tumors that develop in actinicly damaged and immunologically suppressed skin. The acute epithelioma has a greater potential for local tissue destruction and a higher metastatic rate than the typical cancer. The morphology is not dissimilar to the self-healing keratoacanthoma and it is often impossible to differentiate between the two on clinical or histological grounds. An earlier unpublished review in 1976 of 173 patients with lesions having a similar appearance and history found that the histology was reported as keratoacanthoma in 73 (43%) and as a well differentiated squamous cell carcinoma in 59 (35%) patients. Lesions in both groups metastasized and caused tumor related deaths while others regressed rapidly with treatment and a few regressed spontaneously. An in-depth review of this capricious tumor is underway.

Salient Points
Squamous Cell Carcinoma/Acute Epithelioma
Ear and Eyelids

	SCC		Acute Epithelioma	
Pts. 193	169	88%	24	12%
Size > 2cm	56	33%	18	75%
+ve nodes	12	7%	8	33%
Death	9	5%	5	21%
Local control	160	95%	23	96%
3 yr cause specific survival	160	95%	19	79%

Figure 1. Summary of the main differences between squamous cell carcinoma and acute epithelioma.

Cutaneous Lymphomas

Cutaneous lymphomas are uncommon either as the first site of tumor or a late manifestation of disease. Primary cutaneous lymphomas are a heterogeneous group of disorders characterized by dermal infiltrates with cells having their origins in lymphatic tissue. Lymphocytes together with cells of the mononuclear phagocytic system function synergistically for the bodies defense. These heterogeneous cells are comprised of two main groups. These are the B (bone-marrow developed) and T (thymus derived) lymphocytes. There are several subgroups and they are thought to originate from a common cell in the bone marrow. The B-lymphocyte gives rise to the non-Hodgkin's groups of lymphomas whereas the T-lymphocyte develops into mycosis fungoides and the Sezary syndrome which is its leukemic form. During the past year these two major groups have been reviewed.

In Canada there are only about 50 new cases of mycosis fungoides that develop annually. Accordingly a cross-Canada co-operative group has been organized and is being coordinated by the group at McMaster University in Hamilton. This group has the largest Canadian experience with the disease because of the electron beam facilities that have been used to treat the tumor with total skin irradiation. Between 1958 and 1981, 53 patients were seen in this hospital and 46 available for review. The median age was 64 (27-90) years and the median duration of symptoms 7 (2/52-33) years. The male to female ratio is 1.9:1. A variety of treatments from topical nitrogen mustard to combination chemotherapy and spot to half body irradiation have been used. The variable pattern of the disease and long natural history is clearly shown in Figure 2.

Mycosis Fungoides
1958 — 1981 46 pts

Survival:
From diagnosis: 3.4 (2d - 13) years
From 1st symptom: 7.9 (7d - 42) years
From 1st treatment: 4.5 (21d - 42) years

Figure 2.

Only 61 patients with a non-Hodgkin's lymphoma involving the skin as the first sign of disease were identified between 1967 and 1982. Most histological subtypes were represented by the diffuse histiocytic category accounted for 28 (46%) cases. Clinically the lymphoma was confined to the skin in 43 patients. The main sites were the head and neck (28), extremities (13), trunk (9) and involved 2 or more sites in 11 patients. Overall the media actuarial survival was 75 months. For patients with disseminated lymphoma this was 18 months and there were no survivors beyond five years. Patients with disease confined to the skin had a media survival of 159 months and 50% survived ten years (Figure 3). Within this group the significant prognostic indicators were the bulk and site of tumor (Figure 4). No prognostic value for any histological subtype was found. Generalized disease should be treated by combination chemotherapy but local treatment by surgery or radiotherapy is effective for limited cutaneous lymphoma.

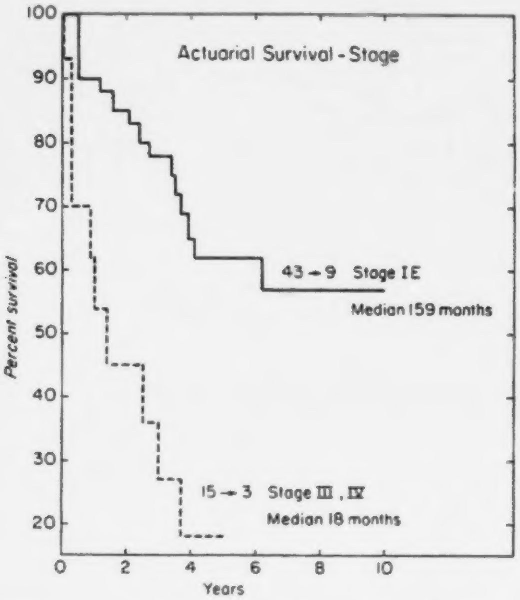

Figure 3. Primary non Hodgkin's lymphoma of skin.

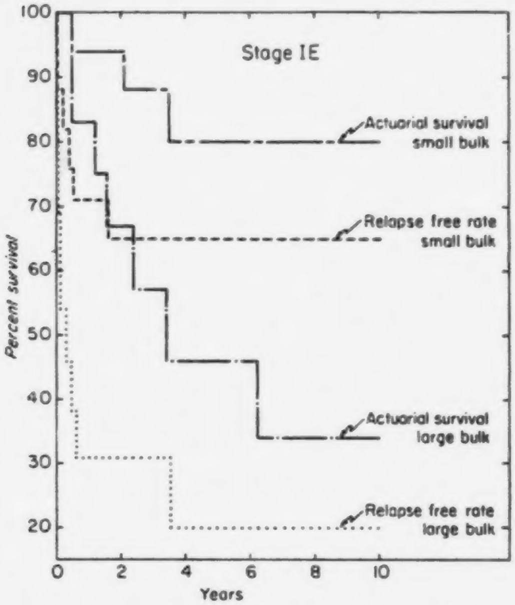

Figure 4. Primary non Hodgkin's lymphoma of skin.

Melanoma

Traditionally malignant melanoma has been regarded as a radioresistant tumor. In recent years it has become apparent that melanoma is not intrinsically radioresistant (1,2,3,4,5). Fractionation regimens using large dose (800 cGy x 3, 0-7-21) per fraction of irradiation have been applied with increasing frequency particularly for patients with lymph node metastases from melanoma (5). A recent update of this experience has been completed. Ninety patients have been treated with the 0-7-21 technique between 1975 and 1981. Forty-eight patients had gross residual or recurrent tumor following previous unsuccessful surgery. 16.5% of this group of patients survived five years following irradiation with the majority of patients dying from distant metastatic disease. The results were poorest in the group of patients with disease more than 3 cm in size.

Forty-one patients were treatment following lymph node dissection or lymph node biopsy who were felt to be at high risk of recurrence within the surgical scar. As a result of the irradiation only 6% of these patients recurred within the surgical field and 35% survived five years. It was concluded that melanoma is not a radioresistant tumor. A randomized controlled clinical trial is required to determine whether adjuvant irradiation will improve survival in patients with lymph node metastases following surgery from malignant melanoma.

For some years we have recognized that lentigo maligna (LM) and lentigo maligna melanoma (LMM) are radioresponsive (6,7). These pigmented lesions are usually large and develop on the head and neck of older people. Doses in the range of 4500 cGy in 10 fractions in 2 weeks controlled 14 of 17 patients with LM and 21 of 23 patients with LMM. Characteristically the lesions take six to 12 months to regress. The cosmetic result is usually excellent.

Kaposi's Sarcoma

Kaposi's sarcoma occurs in two basic types. The classical form of the disease occurs in elderly people of Eastern European Jewish ancestry or from the Mediterranean. This form of the disease pursues an indolent course and is very responsive to low doses of irradiation which is the treatment of choice. Experience in more than 80 patients with the classical form of the disease indicates that more than 80% of patients will respond to a single dose of 800 rads.

The second type of Kaposi's sarcoma is that associated with immunosuppression (AID's, renal transplant patients). The disease in this form is more aggressive and frequently causes the death of the patient due to disseminated Kaposi's sarcoma associated with AID's. Treatment including chemotherapy and irradiation has unfortunately proven not to be very successful and the majority of patients succumb to their disease.

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Gastrointestinal Oncology

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Nearly 800 patients with carcinomas arising in the gastrointestinal tract are referred to the Princess Margaret Hospital each year. Major current research projects include the study of combined radiation and chemotherapy for the treatment of epidermoid cancers arising in the esophagus or anal areas, adjuvant radiation in the treatment of primary carcinoma of the rectum and colon, and the chemotherapeutic management of patients with metastatic colon or rectal cancer.

Carcinoma of the Anal Canal

Although carcinoma of the anal canal is uncommon, these tumors have excited considerable interest at OCI/PMH and elsewhere over the past decade. The development of an effective program of concurrent radiation and chemotherapy, first introduced by Nigro and his colleagues in Detroit, has meant that many patients are now treated by techniques which preserve anal function and avoid the need for colostomy.

This program was introduced at OCI/PMH in 1978. The program differs from the Detroit protocol by combining chemotherapy with radical radiation therapy doses, rather than being intended as preoperative adjuvant therapy. We have recently compared the results in 30 patients treated by combined radiation, 5 Fluorouracil and Mitomycin C with 25 patients treated prior to 1978 by radiation therapy alone (2). The most apparent change is in the improved rate of control of the primary anal carcinoma control rate where combined modality therapy was successful in 93% (28/30), compared to 60% (15/25) treated by radiation alone. Because anal canal cancer tends to remain localized to the pelvis, surgical resection is frequently successful in those patients in whom radiation therapy or combined modality treatment does not control the tumor. As a result, the survival rate has not changed significantly with the addition of chemotherapy to radiation, but the number of patients who have retained anal function has improved noticeably (Figure 1).

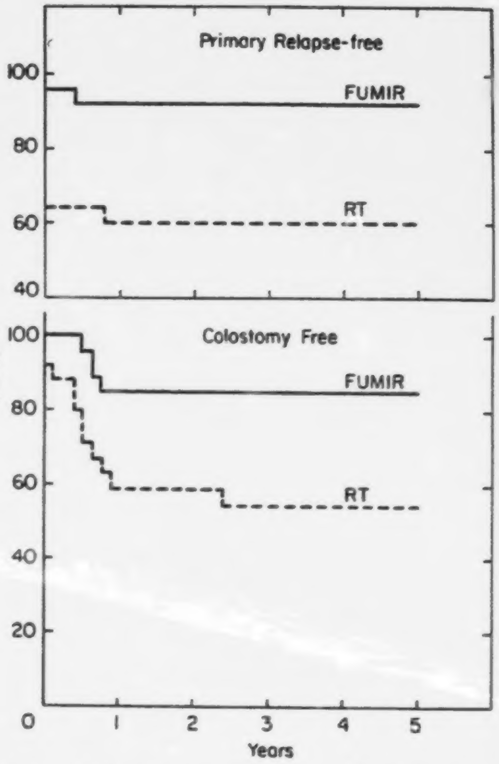

Figure 1. Anal canal carcinoma. Actuarial primary tumor control and colostomy free survival from the date of first radiation treatment for patients treated by radical radiation (RR) or by radical radiation combined with 5-Fluorouracil and Mitomycin C (FUMIR).

We are continuing our clinical studies of concurrent chemotherapy and radiation therapy for squamous cell carcinomas in the gastrointestinal tract and in other sites. Laboratory investigations both at OCI and elsewhere are continuing to establish whether the chemotherapy agents used in this program, 5-Flourouracil (5-FU) and Mitomycin C, interact with radiation therapy as sensitizers, or act independently, so that the apparent improvement in primary tumor control is due to the simple addition of the three cytotoxic therapies.

Carcinoma of the Esophagus

The improvement in primary tumor control rates seen with combined chemotherapy and radiation therapy in carcinoma of the anal canal suggested that this combination might also be of benefit in other squamous cell carcinomas in which failure to control the primary carcinoma was a major problem. In cancer of the esophagus, a retrospective analysis of the experience at the OCI/PMH with radical radiation alone has shown failure at the primary site in up to 80% of patients (1).

The combination of 5-FU, Mitomycin C, and radiation has been evaluated in 35 patients with locally extensive esophageal carcinoma and the results were compared with matched controls from patients treated by radiation alone (3). Both survival and the local relapse-free rates appeared to be improved with the combined modality treatment. The survival rate at 2 years was 28% compared to 15% with radiation alone, and the primary tumor relapse-free rate was 48% compared to 20% (Figure 2).

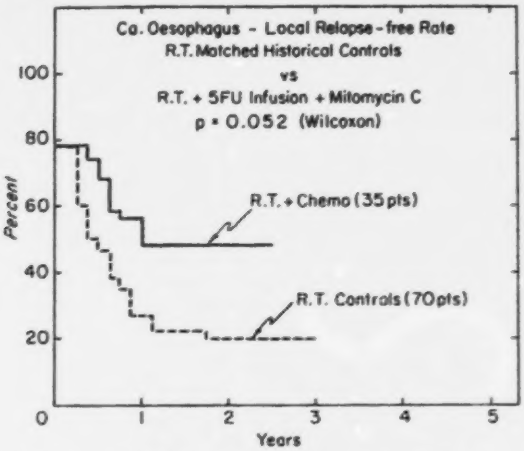

Figure 2. Esophageal carcinoma. Actuarial local relapse free rate for patients receiving radiation (RT) plus chemotherapy compared to the historical control group treated by radiation alone. Each patient treated with RT plus chemotherapy was matched with two historical controls by age, sex, tumor stage, and radiation therapy dose.

Further analysis of this study suggested that a single uninterrupted course of treatment was preferable to split course therapy, and that the inclusion of Mitomycin C did not improve on the results of radiation plus a concurrent 4 day infusion of 5-FU.

At present the Group is involved in discussions for a proposed multi-center trial which would compare radiation alone with radiation plus 5-FU in patients with carcinoma of the esophagus.

Adenocarcinoma of the Rectum

Patients with adenocarcinoma of the rectum have about a 20% to 40% risk of developing recurrent disease in the pelvis, despite apparently complete surgical resection of the primary tumor. These recurrences are difficult to eradicate, and are a major cause of morbidity and mortality in these patients. The OCI/PMH was one of the first to study the use of adjuvant radiation therapy for the possible prevention of pelvic recurrence, and interest in this problem has continued. Recent studies have suggested that relatively high doses of pelvic radiation may be necessary and progress in surgical techniques has made it important that any adjuvant treatment not interfere unduly with the safety of colorectal anastomoses performed in the course of resection of the rectal tumor.

An extended pilot study of preoperative adjuvant radiation has been carried out in collaboration with a number of surgeons in the University of Toronto and in areas served by OCI/PMH. A randomized trial is now being opened in which patients with rectal carcinoma will be randomized to treatment by surgical resection or to resection preceded by pelvic radiation therapy to 4500 cGy in 5 weeks.

Adenocarcinoma of the Colon

At least 50% of tumor recurrences following resection of adenocarcinomas of the colon occur within the abdominal cavity. Until recently efforts to prevent these recurrences have focused mainly on adjuvant chemotherapy but the results have been disappointing.

During the past year, a retrospective analysis of the OCI/PMH experience with total abdominal radiation following the resection of colon carcinoma was complete (4). The outcome in patients who were treated when they were known to have clinically detectable residual carcinoma was disappointing, and it was clear that radiation doses of about 2000 cGy in 4 weeks to the whole abdomen, even with local boost irradiation for another 2000-2500 cGy were not sufficient to control gross residual tumor. However, in 30 patients who were at high risk of microscopic residual carcinoma, adjuvant total abdominal irradiation of 2000-2500 cGy in 4 weeks was well tolerated, and 73% remained relapse free in the peritoneal cavity and tumor bed area.

This preliminary data is now being examined in a randomized study. Patients with an adenocarcinoma of the colon which arises more that 15 cm from the anal verge are treated initially by surgical resection. Those in whom the tumor has penetrated to the serosa, or who have lymph node metastases, are then randomized to receive total abdominal irradiation 2200 cGy in 4 weeks, or are followed regularly with any additional treatment deferred until recurrence is apparent.

5-Fluorouracil and Folinic Acid Trial for Metastatic Colorectal Adenocarcinoma

Beginning in May 1984, Dr. Erlichman and Dr. Fine began a collaborative study with the Tom Baker Cancer Centre in Calgary, Alberta (Dr. Alfred Wong) to evaluate the benefits of 5-FU and high dose folinic acid as compared to 5-FU alone in the treatment of patients with advanced measurable colorectal cancer who had not received previous chemotherapy.

Previous Phase II studies reported from France and from the USA had shown a response rate to the combination in previously untreated patients of approximately 40% and a median survival of 15 months. Both response rates and survival data represent a substantial improvement compared to historical information and to studies at the OCI/PMH with high dose 5-FU and Allopurinol or sequenced Methotrexate and 5-FU.

A randomized Phase III trial has been established to test the Phase II results of 5-FU and Folinic acid against 5-FU alone. In this study, patients are randomized to receive courses of 5-FU 375 mg I.V. bolus injection daily for 5 days, or similar 5-FU doses in which the 5-FU is preceded each day by an injection of 300 mg/m2 Folinic acid.

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Gynecologic Malignancies

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Approximately 800 women with gynecologic malignancies are referred annually to The Princess Margaret Hospital. There is a major emphasis on multiple-modality treatment decision-making involving a tumor-board with participation of gynecologic, medical and radiation oncologists. Principal research projects are clinical with the main focus being in ovarian and cervical cancers.

Cervical Cancer (Thomas)

1. Concurrent Radiotherapy/5-FU + Mitomycin C Pilot Study

A non-randomized study of the toxicity and feasibility of concurrent chemotherapy and radical pelvic irradiation in cervical cancer is nearing completion. It has proved possible to administer the combined modality regimen without apparently increased early or late toxicity. Since an interactive process between the two modalities is postulated, the regimen involves the administration of two 4-day infusions of 5-FU during the radiotherapy, the use of smaller treatment fraction size, (161 cGy) twice daily and radiation treatment during the period of the 5-FU infusions, and avoidance of a treatment interruption ("Split-Course"). The rapidity and completeness of tumor regression appears to be similar to that observed with the use of this regimen for the treatment of squamous cancers in other sites. A matched pair analysis with historic controls has not shown any significant survival or relapse-free improvement. However, a randomized study is planned in the near future.

2. Failure Patterns, Prognostic Factors and Treatment Toxicity

A retrospective survey of patients treated by radiotherapy at The Princess Margaret Hospital is being used to characterize prognostic subgroups, and a comparison between the radiation technique used at The Princess Margaret Hospital with those employed elsewhere is being undertaken, to see whether a modification of presently employed techniques might predict an improvement in therapeutic ratio.

Endometrial Cancer (Bean, Pringle)

A retrospective survey of treatment methods, prognostic factors and sites of relapse is being conducted to ascertain whether management policy changes or prospective clinical trials are warranted.

Ovarian Cancer (Dembo, Sturgeon)

1. A randomised study of two-doses of abdominopelvic irradiation is underway in patients for whom radiotherapy is deemed appropriate as the sole postoperative treatment method. The study objectives are to determine the optimal radiation dosage and to ascertain if a dose-tumor control effect can be demonstrated.

2. A randomised study is underway comparing abdominopelvic irradiation and 3 courses of cisplatin based combination chemotherapy, in patients who have been rendered surgically free of macroscopic tumor by 6 courses of chemotherapy and with bulky residual tumor postoperatively. The study attempts to resolve the conflicting results reported by others concerning the value of radiotherapy after chemotherapy.

3. Tumor Marker NB/70K (Dembo, Urbach (Wellesley Hospital), Malkin (Sunnybrook Medical Center))

A polyclonal rabbit heterosera immunoassay to detect the ovarian cancer antigen NB/70K (a 70K-dalton glycoprotein) in the serum of patients with ovarian cancer is being prospectively studied. Preliminary results suggest the assay may have similar sensitivity and specificity to the monoclonal assay for CA-125, and might show complementarity with CA-125.

4. NCI(C) Phase II Study of Carboplatin (Sturgeon, Fine)

Eighteen patients with tumor relapsing after firstline treatment, were studied for tumor response and toxicity on Carboplatin, an investigational drug, which is a cisplatin analogue. Further participation in Phase II Studies is planned.

Head and Neck, and Ear, Nose and Throat Oncology

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ENT Division

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Epithelial tumors of the upper aerodigestive tract account for about 5% of all cancers and there incident appears to be increasing. About 600 new patients with epithelial tumors of the upper digestive and respiratory tracts are seen annually. These patients are mainly referred by general surgeons with a major interest in the head and neck and otolaryngological surgeons. These two distinct referral patterns have led to separate groups of ENT and Head and Neck Clinics. There is, however, considerable overlap between the groups. Patients are treated by similar protocols and entered into clinical trials. Fortnightly combined conferences are held during which clinical material is reviewed and protocols are developed. Interesting and difficult clinical cases are also presented and discussed. These sessions provide an excellent teaching session for the resident staff in radiation oncology, surgery and otolaryngology.

Head and Neck Division

Two joint weekly clinics are held. The majority of patients have tumors of the oral cavity, salivary glands or metastatic disease in the neck. All new and problem patients are reviewed jointly by a radiation oncologist and surgeon. Ninety percent of the tumors are squamous cell carcinomas with varying degrees of differentiation. Apart from early tumors which are treated surgically, the majority are treated by irradiation, with surgery reserved for failure. Our philosophy for treatment is to use irradiation first and to reserve surgery for persistent or recurrent tumor. This delayed combined approach optimizes both treatment modalities. Failure is defined by obvious or biopsy proven tumor present 12 weeks following radiotherapy. This philosophy enables patients successfully treated by radiotherapy to achieve a good cosmetic and functional result. For salivary gland tumors the primary treatment is surgical excision with removal of the whole gland whenever possible. If the excision is incomplete postoperative radiotherapy is given.

Salivary Gland Tumors

Salivary gland tumors are relatively uncommon and only account for about 3% of neoplasms of the head and neck. Of these 80% occur in the parotid and onehalf are malignant. Between 1958 and 1972 643 patients with salivary gland tumors were identified from the records of this hospital and the Toronto General Hospital. There were 328 malignant and 315 benign cases. For the malignant tumors the first planned treatment controlled the cancer is 145 (44%) patients. The five and ten year actuarial survival rates were 59.4% and 45.6%. The radioresponsiveness of these tumors has been disputed but this review showed similar results for patients whose tumor was completely resected and for those where the resection was incomplete but postoperative radiotherapy was given (Figure 1). We believe that these tumors are radioresponsive and that treatment results can be related to the bulk of tumor. Survival is also related to the histologic type (Figure 2).

Lip Cancer

The lip is the first part of the upper digestive tract. Lip cancers are common and second only to skin cancer as the most common tumor of the head and neck. A retrospective review of 361 patients with carcinoma of the lip seen between 1971 and 1976 was

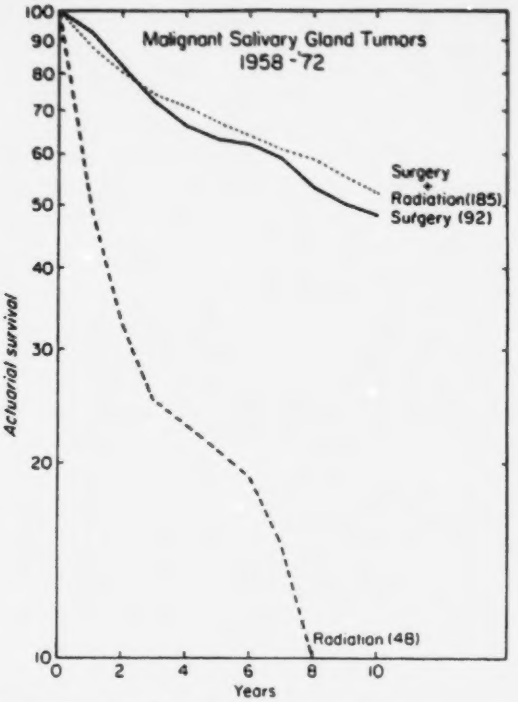

Figure 1. Survival by method of treatment. Postoperative irradiation was valuable when the resection was incomplete

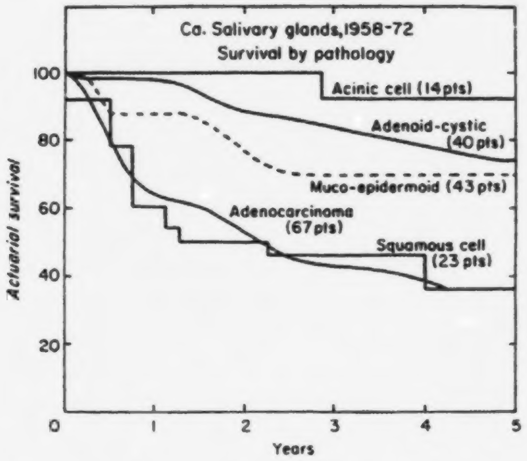

Figure 2. Survival stratified by histology for 187 patients with malignant tumors.

performed. (1) There were 348 squamous cell and 13 basal cell carcinomas with the latter having arisen from the skin of the lip and crossed the vermilion margin. The lower to upper lip ratio was 15:1 and the male to female ration 12:1. The primary tumor was controlled by surgery in 76/85 (89%) patients by surgery and radiation combined in 65/70 (93%) patients, and by radiation alone in 193/206) (94%) patients. Altogether 24 (6.5%) patients developed cervical node metastases and these were controlled in 20 (83%). Tumor related deaths occurred in 11 (3%) patients and the five year cause-specific survival rate was 97%.

Multiple Cancers in the Upper Digestive Tract

Cases of multiple primary carcinomas in the same region and elsewhere in the body are becoming increasingly common. In general there is an increased incidence of similar tumors in the same region and in anatomically related organs due to the effect of the same carcinogens. Among 6203 cases of primary squamous carcinoma of the upper digestive tract seen between 1958 and 1982 648 patients (10.4%) developed two or more independent tumors. Altogether, 761 additional malignancies were observed, with up to five cancers being seen in individual patients. There were 279 patients with prior or synchronous cancer and 409 patients who developed 462 metachronous tumors. There was a substantial risk for developing a second primary cancer in the upper aerodigestive tract (figure 3). Overall the observed to expected ratio was 2.48, specifically 2.32 for males and 2.89 for females (figure 4). Survival rates alone do not adequately reflect the outcome of the first cancer in the upper digestive tract. The development of multiple squamous cell carcinomas is common following successful treatment. The risk is constant and excessive (1321 compared to normal) regardless of time.

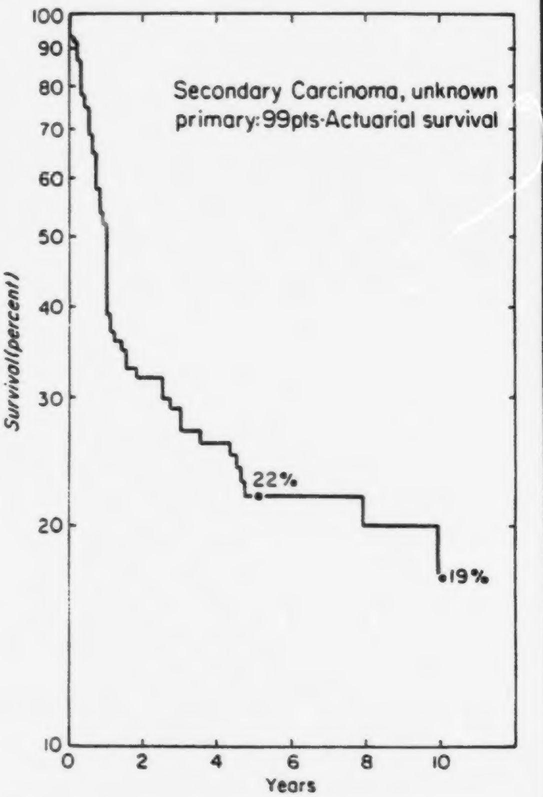

Figure 3. The actuarial survival rate for 99 patients with secondary carcinoma in neck nodes but no known primary tumor. At five years, 22% of patients are alive.

Metastatic Disease in the Neck from an Unknown Primary Cancer

Malignant disease in the neck is common in clinical practice and often the first sign of cancer. The majority of these patients have a primary cancer within the head and neck, but in about 5% of these patients the primary is occult and undetectable. With more meticulus examination the incidence of these patients is declining. Between 1971 and 1982 although 489 new patients with malignant disease were seen, only 144 were classified as having metastatic cancer in the neck with an unknown primary tumor. The results of this review were similar to that of a previous study.(2) The overall five year actuarial survival rate for the first study was 18% and 22% for the second (Figure 3). Patients with cervical metastases in the mid and upper neck fared better than those with disease in the lower neck. It was possible to identify a select group of patients with metastases limited to the upper and middle cervical nodes and radically irradiated. The local control rate was 86% and the five year survival rate 41% (Figure 4). These results are similar to our reported experience of patients with squamous cell carcinoma of the oral cavity. (3) Patients with lower neck disease fared poorly with only 19% surviving five years.

When required, the major head and neck surgery for our patients is mostly done at the Mount Sinai, Toronto General and Toronto Western Hospitals.

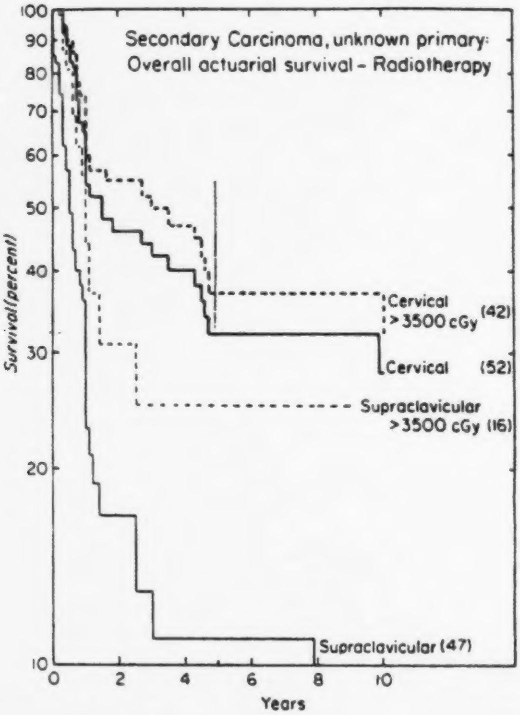

Figure 4. Patients with cervical metastases do better than those with supraclavicular disease. There appears to be an advantage to those treated radically with 3500 cGy or more.

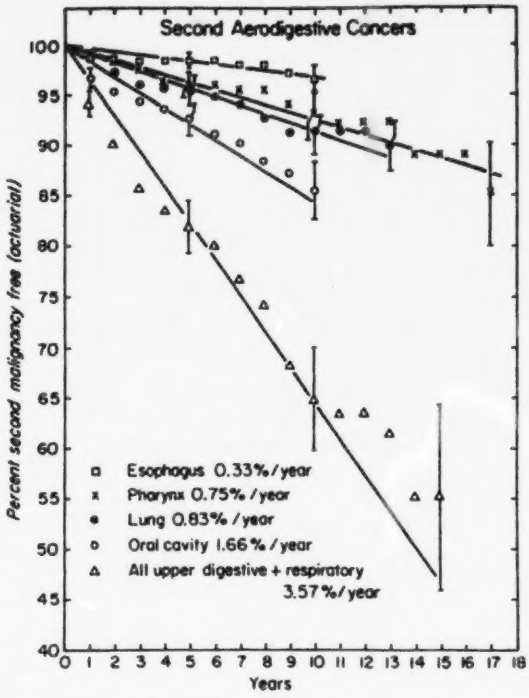

Figure 5. Rate of onset for a second malignancy remains constant from the time of successful treatment of the first cancer.

SUBSEQUENT MALIGNANCY AFTER UPPER G.I. CANCER

		FEMALE	MALE	TOTAL
	OBSERVED	144	318	462
FOLLOW-UP	ACTUAL DATE			
	EXPECTED	49.84	136.82	186.66
	O/E	2.89	2.32	2.48
	MAY 31/82			
	EXPECTED	71.19	187.67	258.86
	O/E	2.02	1.69	1.78

Figure 6. Because of incomplete records the observed to expected ratios for other cancers developing subsequent to the index tumor were calculated from two dates. The patient-years at risk for the actual follow-up date and using May 31, 1982 for all patients known to be alive were 14,792.62 and 19,624.72.

Approaches to the pharynx are difficult. In order to better access pharyngeal tumors a nonrandomized prospective study was initiated to study a midline mandibulotomy (mandible sparing) approach. To date, some 20 patients have been explored in this way and the initial results are encouraging. Radical surgery leaves large tissue deficits and reconstruction has always been a major problem. In the last few years the use of microvascular composite graft constructions has hastened rehabilitation and improved the cosmetic result. Our surgeons, in conjunction with others in the division of plastic surgery, have now treated approximately 90 patients in this manner. The composite graphs are obtained from the iliac crest or foot.

Osteoradionecrosis of the mandible following curative radiotherapy remains a problem. Thirty-two patients with this complication were identified and in 20 surgery was required. Seven of these had the mandible reconstructed using a dorsatis pedis osteocutaneous flap with microvascular anastomosis. Healing was relatively uncomplicated and patients returned to a pain-free life. Although time consuming, this approach is a major advance in the management of this complication.

Uncontrolled head and neck cancers cause difficult clinical problems and severe distress to patients and their families. Unfortunately, after radiation and surgery have failed there is little that can be done to control the cancer. However, a prospective randomized controlled trial on our patients is underway at the Toronto General Hospital. Patients are randomized to receive a combination of cis-platinum, bleomycin and VP 16 with or without radiofrequency hyperthermia. To date some 20 patients have been treated.

ENT Randomised Studies

For the past 3 years the group has been conducting a randomised clinical study of radiation and chemotherapy compared to radiation alone as primary treatment for advanced carcinomas of the larynx and all carcinomas of the hypopharynx. This study is being done in collaboration with the Manitoba Cancer Treatment and Research Foundation Clinic in Winnipeg and the Ontario Cancer Treatment and Research Foundation Clinics in Ottawa and Toronto (Toronto Bayview Centre). This clinical trial is supported with a grant from the National Cancer Institute of Canada. The study design is shown in Figure 1.

One hundred sixty-three (163) patients have been entered on this study to date. It is planned to enter a total of 210 patients. Entry is expected to be completed by December 1985.

The group is also conducting a randomised trial designed to assess the value of elective irradiation of the uninvolved lower neck for patients with carcinomas of the oral cavity and oropharynx presenting with clinically negative neck nodes. In this study patients are being randomised to receive radiation therapy or observation of the uninvolved lower cervical nodes following radical radiation therapy to the primary tumor and uninvolved nodes in the upper neck (above the level of the thyroid cartilage).

ENT Non-Randomised Studies

Because of the low incidence of a number of specific tumors in the head and neck region randomised studies are not possible for all sites. In these situations ie. carcinoma of the nasopharynx, para and nasal sinuses, juvenile angiofibroma, and glomus tumors, treatment protocols have been developed. The results of these protocols are monitored by periodic failure analysis. Such analyses provide a method of review of treatment results for these rare tumors and allow protocol changes aimed at improving results to be made over time.

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Leukemia Trials

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(See also the section on "Normal and Leukemic Haemopoiesis")

Acute Myeloblastic Leukemia Results of Clinical Trials (Curtis)

The present clinical trial for the management of patients with AML at The Ontario Cancer Institute incorporating The Princess Margaret Hospital (OCI/PMH) involves the use of megadoses of cytosine arabinoside (Ara-C) for remission induction. In addition, monthly courses of a low-dose Ara-C schedule are used for maintenance treatment. This trial, the fourth of a series of sequential trials of therapy in AML, is the first study planned on the basis of laboratory research at OCI/PMH. Successful completion has validated the laboratory research and provided new directions for clinical and laboratory investigations.

Laboratory studies reported in detail elsewhere in this report (See "The Blast Cells of Acute Myeloblastic Leukemia") have shown an association between the sensitivity of blast cells in suspension culture in clinical outcome. These studies are an extension of investigations that demonstrated a possible unique mechanism of action for Ara-C. Alone of the agents tested, Ara-C reduced the self-renewal capacity of blast cells in culture termed PE_2 (plating efficiency in secondary cultures). In previous sequential trials of maintenance therapy of AML at this hospital, PE_2 has been the most powerful prognostic attribute predictive of outcome of remission induction, the duration of first remission, and duration of overall survival.

To date 45 patients have been admitted to the clinical trial of high-dose cytosine arabinoside for adult patients with AML. The results of remission induction therapy are evaluable for 43 of these patients. Successful remission induction has been achieved in 29 patients (68 per cent). This is compared with a 51 per cent response rate in 81 patients treated in the preceding study (ACT) in which remission was induced with 3 drugs, doxorubicin, Ara-C and 6-thioguanine. Preliminary data suggest that the duration of first remission and overall survival achieved with high-dose Ara-C are at least as good as those obtained using multi-drug regimens.

These clinical studies demonstrate the importance of close collaboration between the laboratory and the clinic. They also provide a model for the development of clinical research for other disease sites. The results of remission induction for adult AML have improved to the extent that increased emphasis must be given to designing more appropriate methods for maintenance treatment. For the laboratory, an objective is to improve our understanding of leukemic hemopoiesis during the remission phase of acute leukemia.

Chronic Granulocytic Leukemia: A Trial of Recombinant α-2 Interferon (Bergsagel, Messner, Stewart)

During the chronic phase, chronic granulocytic leukemia (CGL) responds to treatment with many chemotherapeutic agents with a fall in leukocyte count, a rise in hemoglobin, reduced splenomegaly and a marked improvement in well-being. Despite this treatment there is a progressive increase in the growth rate of the leukemic population and failure of normal hemopoiesis, manifested by anemia and thrombocytopenia, leading to the terminal acute blast phase. Current therapeutic approaches have relieved symptoms, but have not prolonged survival.

Interferons have been found to inhibit colony formation in cell culture by normal hemopoietic precursors and the leukemic blast cells equally well. However, interferon reduces the capacity of the leukemic cells to self-renew. This data suggests that interferons may be useful agents for maintaining a remission, but not for remission induction.

We are testing the ability of recombinant alpha-2 interferon (r-α-2 IFN) to prolong busulfan-induced remissions of CGL patients. No therapy is given during the first remission during which the leukocyte-doubling time and the proportion of mixed colony-forming units in cell cycle is determined. the r-α-2 IFN is begun. The leukocyte doubling-time and the proportion of mixed colony-forming cells in cell cycle during r-α-2 IFN treatment is prolonged by interferon we would expect both remission duration and survival to be prolonged. In addition, the proportion of Ph^{1}-positive metaphases will be determined before and after interferon treatment. The r-α-2 IFN is administered subcutaneously three times per week by the patient, and has been well tolerated.

Hairy Cell Leukemia: A Trial of Recombinant α-2 Interferon (Bergsagel, Stewart)

Hairy cell leukemia (HCL) is a chronic disease marked by marrow failure (anemia, neutropenia and thrombocytopenia), splenomegaly and severe, recurrent infections. Splenectomy may produce a remission, but when relapse occurs there was no other effective form of treatment until the interferons were introduced. Treatment with recombinant α-2 interferon (r-α-2) IFN. Patients who achieve a stable recovery of marrow function are randomized to continue r-α-2 IFN or to discontinue therapy until relapse. Patients administer r-α-2 IFN to themselves subcutaneously. This treatment is well-tolerated.

Lung Cancer Studies

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Over 1,000 patients with carcinomas arising from the lung are referred to The Princess Margaret Hospital each year. Some of these are referred here for radiation only or occasionally for chemotherapy only. As many as possible are put on clinical trials.

There is an active multidisciplinary group dealing with lung cancer at The Princess Margaret Hospital. In addition, there are individuals in many of the disciplines, particularly surgery, pathology and medical oncology at all the teaching hospitals in Toronto, allowing for close cooperation. Over the years, this led to sufficient cooperation that trials were able to be carried out at The Princess Margaret Hospital alone, city-wide, nationally (usually through the National Cancer Institute of Canada), or Internationally in cooperation with American Centers and more recently European centers through the Lung Cancer Study Group (Funded by the NCI-US). Clinical trials are being carried out in all histologies and all stages including the adjuvant setting in patients with completely resected surgical disease. In addition to the end results of therapy, other information about sites of failure, pathology and some biological data have come from these trials leading to a better understanding of the disease as well as providing an appropriate basis for the planning of future clinical trials.

Small Cell Lung Cancer Studies

1. NCI(C) Studies

a) BR-3: This study comparing alternating and sequential chemotherapy regimens employing cyclophosphamide, Adriamcyin and cisplatinum has accrued its required number of patients. Patients receive three courses of both regimens either using alternating approach or three of each, beginning with the CAV regimen as the sequential arm. The data so far shows a very slight increase in the complete remission rate on the alternating arm but no survival benefit. There was slightly more toxicity on the sequential arm.

b) BR-4: This compares six courses of CAV to this combination alternating with VP-16 and cisplatinum in patients with extensive small cell lung cancer. This study has also accrued the required number of patients and has been stopped. There is early data suggesting there may be both a response and survival benefit to the alternating regimen. This may suggest that the Goldie-Coldman hypothesis is correct. Another possible explanation is that the VP-16 and cisplatinum is the better treatment and that the alternating approach is not what has improved the outcome.

c) BR-6: This trial has just begun patient entry. Patients with limited disease receive alternating CAV and VP-16 cisplatinum for a total of six courses. Thoracic irradiation is either given early (during the second course of chemotherapy) with VP-16 and cisplatinum or at the end of therapy. Prophylactic cranial irradiation is used in this study as it was in Dr-3 and DR-4. It is hoped that giving early thoracic irradiation might improve the results of an alternating regimen in this disease.

2. Lung Cancer Study Group (LCSG) Trials

The Lung Cancer Study Group (an international co-operative group funded by the NCI (U.S.) is continuing its small cell study (832). Physicians at The Princess Margaret Hospital as well as at other Toronto institutions are entering patients on this study. Patients with limited disease receive five courses of CAV and if clinically resectable, are randomized to surgery or not. They all receive prophylactic cranial irradiaiton and thoracic irradiation but no further chemotherapy. The value of surgery as an addition to chemotherapy and radiation is being tested in this trial. A European group (EORTC) will also enter patients on this trial.

Non-small Cell Studies

1. Current Lung Cancer Study Group Trials

a) Protocol 791: This involves patients with microscopic or macroscopic residual disease after attempted complete resection. Patients were randomized to receive either radiation lone or radiation plus chemotherapy with cyclophosphamide, adriamycin and cisplatinum (CAP). The combined modality treatment with chemotherapy plus radiation has been shown to be superior, both in disease-free and overall survival.

b) Protocol 772: This study involves patients with totally resected Stage II and II adenocarcinoma and large cell carcinoma of the lung. It compares adjuvant treatment with CAP versus immunotherapy (intrapleural BCG and levamisole). This trial has been completed and shows a significant relapse-free and overall survival for the chemotherapy arm. The immunotherapy arm has results that are very similar to concurrent historical controls looked at two institutions (The Massachusset's General Hospital and Sloan-Kettering Institute in New York City). Unfortunately, a no treatment control was not included in this trial.

c) Protocol 773: This study involves totally resected patients with Stage II and III squamous cell carcinoma of the lung. Patients were randomized to receive adjuvant radiotherapy or no additional treatment. Accrual to this study has been discontinued. Although no effect on relapse-free or overall survival was shown, there appears to be a significant reduction in local relapses in the chest in the patients randomized to receive the radiation therapy.

d) Protocol 801: This study deals with totally resected patients with T_1N_1 and T_2N_0 Stage I non-small cell lung cancer. This patients are randomized to receive four courses of CAP or no additional treatment. This study is still accruing patients.

e) Protocol 831: This protocol is a pilot study dealing with patients who have non-small cell lung cancer that is technically unresectable but is quite limited in the chest. The patients receive a total of three courses of CAP, two concurrent with split course radiation therapy in a hope to reduce the tumour burden sufficiently to make them surgically resectable. Accrual patients have been able to be resected but the treatment seems to be quite toxic. Longer follow-up will be necessary to draw any conclusions from this trial.

f) Protocol 841: This deals with patients with resectable non-small cell lung cancer involving the chest wall. Patients are randomized to receive radiation or no additional treatment. This study is continuing to accrue patients.

2. New Lung Cancer Study Group Trials

a) Protocol 772 & 773 will be replaced by new trials. This population includes stage II and III totally resected non-small cell carcinoma of the lung. Those with adeno and large cell carcinoma will be randomized to CAP or no additional treatment with the possibility of receiving late CAP on relapse. Patients who have squamous histologies will be randomized to receive CAP or no additional treatment and will be offered radiation therapy if they fail locally.

b) Protocol 831 will be replaced with a new study. This will involve patients who have technically unresectable non-small cell lung cancer that is limited to the chest. Patients will receive 5-FU infusion and cisplatinum along with radiation in an attempt to make them surgically resectable.

c) A pilot study on pleural pneumonectomy in mesothelioma patient is being planned. There will also be a registry of all mesothelioma patients throughout the Lung Cancer study Group.

d) A study using monoclonal antibodies to small cell lung cancer may be designed to test the value of this approach as a diagnostic imaging procedure in this disease with Dr. Paul Bunn from Denver Supervising the study.

3. NCI of Canada Studies

a) BR-5: This study is a three arm trial comparing CAP to vindesine plus cisplatinum versus best supportive care in patients with extensive non-small cell lung cancer. It is expected that about one more year will be required to finish accrual to this study. The two questions being asked are whether chemotherapy is of any value in this group of patients and whether the two regimens differ either in their effectiveness of their toxicity.

4. Other Non-Small Cell Lung Cancer Studies

a) Nutritional Assessment Study: This study funded through the NCI (U.S.) supervised by Dr. Jeejeebhoy and Dr. Evans at Toronto General Hospital has now completed accrual. This study tried to test the value of nutritional intervention in patients with extensive nonsmall cell lung cancer treated with vindesine and cisplatinum. Patients received two different forms of nutritional intervention or no additional treatment. The data shows no benefit to the nutritional intervention.

b) The value of magnetic resonance imaging (MRI) in potentially resectable non-small cell lung cancer: This study has been under way through the co-operation of surgeons at the teaching hospitals in Toronto. This compares the value of x-rays with tomography, CT and MRI in patients who will have mediastinoscopy plus or minus a thoracotomy. This study has accrued in excess of 150 patients and should soon be able to tell us which is the best diagnostic procedure. Dr. Poon from our radiology department is also having other radiologists in the city view the films to look for any interobserver variability.

The Lymphoma Program

The current Lymphoma Program was initiated in 1982 with the goal of parallel development of a prospective data management system, a coordinated policy of disease investigation and treatment, and a clinical: research interface to permit a more fundamental analysis of lymphoma cell biology.

Lymphoma Data Management

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G. DeBoer, Ph.D., Head, Department of Biostatistics
S.B. Sutcliffe, M.D., Radiation Oncologist/Senior Scientist

The data management system was designed to provide an accurate, current account of lymphoma practice at The Princess Margaret Hospital.

The system comprises two sections — a "forms-oriented" basic data entry and retrieval system, and an analysis system involving DATATRIEVE (D.E.C.) and other statistical packages.

Biographies, therapy, and follow-up files are entered on all patients with malignant lymphoma referred to PMH for management within 6 months of initial diagnosis and/or therapy. Since commencing patient information entry in September 1982, 591 individual patient records have been filled. Preliminary data analysis is currently being performed. Modifications to provide prospective identification of clinic attendance and scheduled investigations, and edit checks to ensure the validity of entered data are being incorporated into the system.

The Clinical Program

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P. Fitzpatrick, M.B., Radiation Oncologist
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J. Curtis, M.D., Medical Oncologist
R. Hasselback, M.D., Medical Oncologist
I. Quirt, M.D., Medical Oncologist
J. Sturgeon, M.B., Medical Oncologist
T.C. Brown, M.D., Pathology
T. Chua, Biostatistics
D.F. Rideout, M.B., Radiology

1. Hodgkin's Disease

Following a detailed retrospective analysis of outcome following radiation therapy for clinical stage I and II Hodgkin's disease for the period 1968-1977, guidelines for investigation and treatment of localised disease were developed. The management strategy was based upon identification of clinical and histopathological attributes of established independent prognostic value at presentation. (1, 2) A prospective application of these guidelines to determine the optimal role of radiation therapy and combined modality therapy for patients with localised disease is ongoing, and comparison of results with those of centers employing routine surgical staging may clarify the role of laparotomy in standard management of early Hodgkin's Disease.

Members of the Lymphoma Group collaborated in the development of the N.C.I.(c) Hodgkin's Disease IV Study and contribute patients to its accrual. This study compares two forms of alternating sequence chemotherapy for patients with Stage IIIb and IV disease with the intention of defining the most effective and least toxic therapy for this patient population. It is anticipated that a national accrual of eligible patients over a 5-year period will be necessary to answer this question.

2. Non-Hodgkin's Lymphoma

The experience with management of localised non-Hodgkin's lymphoma with radiation therapy has been analysed for the period 1967-1978. (3, 4) In addition, analyses of outcome following radiation therapy for specific extranodal presentations of localised lymphoma have been undertaken. Guidelines for the management of patients with localised non-Hodgkin's lymphoma involving nodal and extranodal sites according to multiparameter prognostic groups are under development. This approach should define the optimal role of radiation in localised non-Hodgkin's lymphoma, and permit evaluation of chemotherapy with or without radiation in patients with localised disease who are at high risk for relapse.

Participation in the N.C.I.(c) LY-3 study to define the importance of adriamycin dose in an intensive combination chemotherapy protocol (B.A.C.O.P.) for patients with advanced highgrade lymphoma continues.

Patients are also entered into N.C.I.(c)-sponsored Phase 2 studies of investigational new drugs in patients with recurrent or refractory non-Hodgkin's lymphoma. A study of spirogermanium has been completed, and two new agents, acivicin and menagarol, are currently under investigation.

3. Myeloma

Since 1977, patients with untreated myeloma have been entered into the NCI-C My 2 study. This study was designed to assess the value of maintenance therapy in patients achieving a stable response with melphalan and prednisone. Although the median duration of remission was longer in those receiving maintenance, those on no maintenance frequently achieved a second remission thereby rendering total duration of remission and survival comparable for the two groups. Despite differences in the total amount of melphalan administered to the two groups, there was no significant differences in the incidence of leukemia to date.

Eligible patients are now entering the NCI-C My 4 study designed to test the value of a diphosphanate (Didronel) in maintaining the skeleton in this disease.

The Research Program

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T.C. Brown, M.D., Pathologist-in-Chief
S. Eakins, R.T., Laboratory Technologist
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M. Tweeddale, M.D., Research Fellow, Division of Bioresearch
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1. The Lymphoma Phenotyping Laboratory (Smith, Booth, Mason, Eakins, Brown, Miller, Ehmnan, McCulloch, Quirt, Patterson, Sutcliffe)

This laboratory was designed to integrate the standard histopathological evaluation of lymphoma biopsy specimens with functional and biological examination based upon flow cytometric assessment of surface phenotype and proliferation kinetics of viable lymphoma cells. During the first year of operation, the laboratory has received over 50 specimens for analysis. The independent prognostic value of functional characteristics of lymphoma cells may be explored given standardisation of treatment options, however it is recognised that as a tertiary referral centre, patients undergoing functional characterization of biopsy material may represent a minority of the population receiving therapy at PMH.

The centralized receipt and processing of material within the Phenotyping Laboratory has facilitated the development of two other research programs.

2. The Use Of Molecular Probes To Identify Clonal Populations And The Identification Of Aberrant Gene Rearrangements In Lymphoma Cell Populations (Zalcberg, Friedlander, Bailey, Minden, Messner, Tweeddale)

Molecular probes to demonstrate rearrangement of genes for immunoglobulin and the T-cell receptor have shown a high degree of correlation with surface phenotype analysis. In several biopsy specimens, probes to detect gene rearrangement have defined a clonal population comprising a minor component of the cell population thereby clarifying ambiguities inherent in surface phenotype profiles. The general utility of immunoglobulin gene/T-cell receptor gene rearrangement for classification of lymphoid malignancies has thus been confirmed.

This technology has also permitted the identification of biclonal disease ie. discordant rearrangements in geographically or temporally unrelated biopsy specimens from the same individual. The issue of inherent susceptibility to more than one type of lymphoid malignancy or the evolution of separate clones from one common progenitor cell is thereby raised, and will form the basis of further investigation.

Cytogenetic analysis has demonstrated certain characteristic translocations associated with malignant lymphoma. A correlation exists between aberrant immunoglobulin gene rearrangements and currently recognised chromosome translocations. The detection of such aberrant rearrangements may lead to the identification of other oncogenes in lymphoma cells.

The application of molecular probes for immunoglobulin or T-cell receptor gene rearrangements to fixed tissue sections (insitu hydridisation) is being applied to two areas:

a) The architectural localization of the malignant clone in tissue and bone marrow specimens. This has particular application where low levels of neoplastic involvement are encountered thereby rendering standard histopathological assessment subject to interpretational uncertainty.

b) The study of immunoglobulin gene, T-cell receptor gene, and growth factor (interleukin-I, interleukin-II) messages in the Red-Sternberg cells of Hodgkin's disease.

3. Cell Culture Examination In Patients With Malignant Lymphoma (Tweeddale, Messner, Lim, Jamal, Benchimol, Minden)

a) Development of a culture system for clonogenic precursors

A culture system for lymphoma and myeloma cells has been developed to identify growth characteristics that define patients at high risk for early death with standard therapy. Prolonged culture has been achieved with cell suspensions form patients with highgrade lymphomas, and subsequent review has demonstrated a strong correlation between sustained growth invitro and poor clinical outcome. (5)

b) Evaluation of cell cultures from patients with lymphoma

Detailed study of cell cultures have indicated that:

— Growth patterns from patients with high grade lymphoma are heterogeneous.

— The majority of cultures do not require ancillary growth factors for sustained proliferation.

— Cultures demonstrating autonomous growth may replace the need for exogenous growth factors in cultures that would otherwise fail to exhibit sustained proliferation.

— Lymphoma cell colonies can be propagated as cell lines with retention of stable phenotype. In a small number of cases where chromosomal abnormalities have been defined, an aberrant gene rearrangement has been detected.

— Cultures demonstrating sustained growth have high levels of P-53 protein

Future studies will address the mechanism of sustained growth in culture, the correlation of phenotype with cell culture characteristics using an expanded reagent panel to establish whether specific phenotypic profiles identify high-risk patients, to examine the role of P-53 as a marker of proliferative potential and the basis of its correlation with growth in culture, and to determine whether growth pattern is defined by specific genetic abnormalities.

The demonstration that growth characteristics in-vitro following initial biopsy predicts failure on standard therapy many provide a basis for selection of high risk patients for novel treatment approaches.

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Veterinary Oncology

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Although there are at least 20 radiotherapy centers for treating animals in the United States there are currently none in Canada. A conventional radiation unit at the Ontario Veterinary College at Guelph became worn out and funding was not available for replacement. In the forseeable future it is hoped to be able to obtain decommissioned radiation units from Ontario radiotherapy centers for installation at Guelph. During the past 18 months there has been collaboration between the Department of Radiation Oncology and the Department of Clinical Studies at the Ontario Veterinary College at the University of Guelph. For some twenty years histological sections from animal tumors have been reviewed on an ad hoc basis by the pathology department of The Ontario Cancer Institute incorporating The Princess Margaret Hospital and on several occasions there have been informal discussions with the veterinarians concerning cooperative studies in the treatment of animal tumors. However, it wasn't until 1983 that the first joint program for treatment of canine lymphoma was established.

Malignant lymphoma is one of the more common neoplasms encountered in animals. It is the most prevalent type of malignant neoplasm in domestic animals and has many similarities to the malignant lymphomas of man. In 1971 half-body irradiation (HBI) was developed at The Princess Margaret Hospital (1). Among the various tumors treated by this method were patients with malignant lymphoma. Good responses were noted and several patients had long unmaintained clinical remissions with one patient being alive and free of disease after 10 years. Improvements in treatment, especially with combination chemotherapy, prevented the further exploration of half-body irradiation as treatment for malignant lymphoma. Therefore it was natural to collaborate with the veterinarians at Guelph in the treatment of canine lymphoma.

Dogs with malignant lymphoma were investigated at Guelph with studies that included blood work, serum biochemistry, lymph node biopsy, bone marrow biopsy, sometimes a liver or spleen biopsy and radiographs of the chest and abdomen. The dogs were clinically staged into groups 1-5 and the histology classified. The animals were irradiated on Saturday mornings at The Princess Margaret Hospital. The body was divided into cranial and caudal halves by a line joining the 13th thoracic vertebra to the xiphisterum and the dogs anesthetized. A midplane dose of 700 cGy was delivered to one-half of the body through lateral opposing fields using the Hemitron cobalt unit. The side with most disease was treated first and four weeks later the other half was irradiated.

To date 14 dogs with advanced lymphoma have been irradiated. A measurable response, sometimes with the complete disappearance of all disease, was noted in 11/14 (78%). In the majority, however, the tumor recurred rapidly in the interval between treatments or soon after therapy was finished. This recurrence pattern is similar to that seen when treatment is discontinued following induction chemotherapy. Seven (50%) dogs experienced moderate respiratory or hematologic problems. Many of the dogs had extensive (Stage 5) high grade lymphoma and in this group HBI proved ineffective. We think that HBI may be beneficial as a cytoreductive agent either before or following combination chemotherapy. Further work is required in this respect together with different doses of radiation.

Cough and diarrhea were noted as side effects of radiation in some animals and so we decided to irradiate eight normal dogs by HBI using doses of 7 and 800 cGy. These treatments were well tolerated and at a medium followup of 10 months no complications have been observed.

On some occasions we had the opportunity to examine six dogs using the CT scanner. These animals, still anesthetized, were scanned in both the lateral and prone positions. This enabled us to, study the whole body and especially the lymph nodes, liver, spleen and lungs.

Advantage was taken of the opportunity to perform liver and spleen scans as well as pedal lymphoscintigrams in eleven dogs, six normal and five with lymphoma. The latter investigation was undertaken in order to study the abdominal lymphatics in view of the high sensitivity and specificity demonstrated for this technique in an earlier study of dogs with mammary carcinoma (2).

A pilot study using an ultrasound hyperthermia system and associated thermometry has been carried out at Guelph. In due course it is hoped to treat some animal tumors by this method in combination with radiotherapy or chemotherapy.

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Normal and Leukemic Hemopoiesis

The Blast Cells Of Acute Myeloblastic Leukemia

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Two reasons dictated the choice of the blast cells of acute myeloblastic leukemia as a model system for cancer in general. First, blast cells can be obtained easily from patients without risk. Second, a number of methods are available for their study; these include tissue culture techniques, phenotypic analysis of the cells using well defined reagents; and, of great importance, a strong link between laboratory and clinical studies provided a powerful way to validate and apply new knowledge.

Blast Cells In Tissue Culture

We now use two tissue culture methods for studying blast cells outside the body. The first is a clonogenic assay; in it, single blast cells give rise to colonies in methylcellulose cultures in the presence of one or more growth factors. Cells can be recovered from colonies, and a minority will form secondary colonies on replating. These observations showed that the blast population could be considered as a lineage maintained by stem cells capable of self-renewal. However, the majority of the cells in colonies were end cells without extensive growth capacity. Thus, the clonogenic assay detected primarily terminal divisions; self renewal could be seen only be the replating procedure; this was of limited use, since secondary colonies usually did not contain new clonogenic cells.

The second culture method is newly discovered. (1) Dr. Nara found that blast cells would grow in suspension culture, provided a high cell density was maintained, and suitable growth factors were provided. Growth was assessed using the clonogenic assay and could be expressed as increased numbers of blast stem cells. Subcultures were made after 4 to 7 days; exponential growth could be maintained for times that varied from patient to patient. An example is given in Figure 1; in this experiment, blasts were recultured at 4-day intervals and the cumulative increase in clonogenic cells plotted as a growth curve.

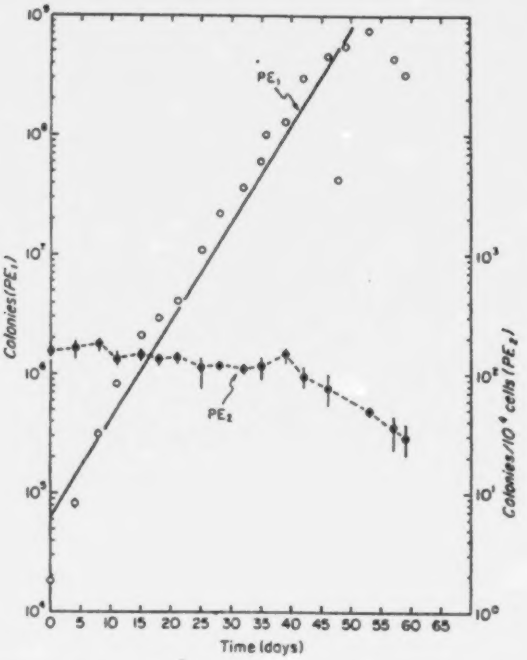

Figure 1. A cumulative growth curve of PE_1 when Blast cells were transferred every 4th day. The growth curve shows a significant exponential form ($r=0.99$, $p<0.01$). This doubling time was three days. PE_1 and PE_2 were maintained for 50 days and 42 days respectively.

It is evident that exponential growth was maintained for 50 days. Evidence was obtained that the growth of blast stem cells reflected their renewal capacity. Thus, the suspension assay was complementary to the methylcellulose method; while the latter depended on terminal divisions, the former displayed directly stem cell self-renewal.

Growth Factors

Both culture techniques required growth factors. Several laboratories have provided evidence that growth factors are the products of single genes, sometimes genes with importance in the etiology of cancer (oncogenes). Dr. T. Hoang initiated studies directed towards the purification and molecular cloning of factors required for blast cell growth. She was encouraged in this endeavour by two important findings. First supernatants from a bladder carcinoma cell line, HTB9, stimulated blast growth both in methylcellulose and in suspension. Second, by comparing various growth factors for their effects on blast cells, she found convincing evidence that the stimulator of blast progenitors was not identical with any known factors active on hemopoietic progenitors. HTB9-conditioned medium provided a constant rich source from which leukemic blast cell growth factor (LBGF) could be purified, while the possibility that LBGF was a unique bioactive molecule made purification a high priority. Using four separate biochemical methods, Dr. Hoang has achieved purification to homogeneity, as judged by a single band after polyacrylamide gel electropheresis.

Complementary experiments have been initiated in collaboration with scientists at the Genetics Institute in Boston. These workers have prepared expression libraries from cDNA obtained from LBGF-producing cells. Following transfection, cos monkey cells produce transient proteins encoded by cDNA fragments in the library. By screening cos supernatants, we hope to identify the gene responsible for LBGF. Initial experiments have been encouraging. If an amino acid sequence can be obtained from the purified protein and a nucleic acid sequence from the cloned gene, a power approach will be available to understanding the molecular control of blast proliferation.

Lineage Infidelity

In some instances single blast cells can be identified that express simultaneously, markers usually associated with more than one lineage. This phenotype has been called "lineage infidelity", to contrast it with the faithful patterns of differentiation seen in normal lineages. Patients whose blast populations included double-marked cells had a poor response to treatment, a clinical observation that supported the validity of the detection of the lineage infidelity phenotype.

The interpretation of lineage infidelity has been controversial. Some have suggested that the presence of markers of more than one differentiation pathway on signal blast cells represents persistence of a phenotype found in the earliest stem cells; its presence in blast cells, then, would provide evidence for their origin by transformation of such stem cells. We have proposed an alternative view; that lineage infidelity is a manifestation of the abnormal gene expression required for a novel blast lineage to be assembled from components of normal differentiation programs.

We have probed the issue further by using methods for detecting components of differentiation programs that did not depend on the recognition of immunologically-defined markers. Dr. G. Cheng used hydrocortisone sensitivity as a way of distinguishing between myelopoietic and lymphoid programs. He showed first that lymphoid colony formation was highly and uniformly sensitive to the hormone, while granulopoiesis proceeded uninhibited even in the presence of large hydrocortisone concentrations. When blast progenitors were tested, marked patient-to-patient variation was found. Moreover, there was a significant association between hydrocortisone sensitivity and failure to achieve remission. The findings were interpreted to mean that hydrocortisone sensitive blasts followed differentiation programs that included lymphoid components; the presence of such components in the programs of AML blasts was considered to be a manifestation of lineage infidelity, one that had the same poor prognostic significance as the phenotype of double-marked blast cells detected using immunological reagents(2).

Clinical Trials

The laboratory studies of AML blasts have always been closely integrated into clinical trials of chemotherapy. These will be described in more detail elsewhere in this report ("Acute Leukemia — Results of Clinical Trials"). In the present context, it is notable that the most recent trial, employing high dose arabinoside (Ara-C) as a single agent for induction and maintenance, has given an improved response rate, compared to previous regimens using multiple drugs. In addition to its general cytotoxic effects Ara-C was shown to reduce the plating efficiency of blasts obtained from primary colonies. This finding was interpreted to mean that Ara-C inhibits self-renewal specifically. Additional support for this view has been obtained using the suspension assay. Growth of clonogenic blasts in suspension was found to be much more sensitive to Ara-C than colony-formation in methylcellulose. No equivalent difference was seen when adriamycin was compared under the two conditions. Furthermore for a small subgroup of 15 AML patients, where Ara-C survival curves were available for cells tested both in suspension and methylcellulose, a significant association was found between drug sensitivity in suspension, but no such correlation emerged when sensitivity in methylcellulose was examined. High dose Ara-C was chosen as the single agent to be used in this protocol, in part, because of the laboratory finding that it was active against blast self-renewal. The new observations support this conclusion. The improved results obtained in the trial are evidence of the value of interface research, where a close correlation is maintained between clinical and laboratory studies.

Conclusion

In conclusion, during the last year, a new culture method has been introduced into our armamentarium for examining AML blasts. The method improves our ability to study self-renewal. We have begun to apply molecular methods to the delineation of the controls on blast proliferation. The concept of lineage infidelity has been extended beyond its applications to immunologically defined blast phenotypes. Most important, evidence is accumulating that knowledge of blast properties can be applied successfully in devising new therapeutic strategies (3).

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Genetic Changes In Leukemic Cells

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The focus of the laboratory is in two areas. The first is to apply the techniques of molecular biology to clinical problems. The second is to determine the genetic changes that have occurred in leukemic cells and how these might contribute to the malignant state.

Origin Of Hemopoietic Cells Following Bone Marrow Transplantation

Following bone marrow transplantation the blood cells that are produced are of donor origin. There has been controversy as to whether the supporting cells of hemopoiesis, the stromal cells, are of donor or recipient origin. In collaboration with Dr. H. Messner's laboratory we have investigated this question. Using restriction fragment length polymorphisms we have been able to show that the stromal cells are of recipient origin. This same technique has proven of value in determining the origin of leukemic relapse following bone marrow transplantation. In one patient chromosome analysis indicated that leukemic relapse was of donor origin while the restriction fragment length polymorphism analysis revealed that the relapse was of recipient origin.

Rearrangement Of The T-Cell Antigen Receptor In Leukemia

Recently the beta chain of the T-Cell antigen receptor was isolated by Dr. T. Mak. In collaboration with him and Drs. Gelfand, Ha, Hozumi, Cheng and McCulloch we have studied the structure of this gene in various forms of leukemia. We have found that there was rearrangement of the T-Cell antigen receptor. This finding may be evidence of aberrant gene regulation in leukemic cells or may indicate that such rearrangements can occur in normal non T-cells. Which of these hypothesis is correct is now under investigation.

Classification Of Lymphoma By Immunoglobulin And T-Cell Antigen Receptor Rearrangement

In collaboration with Dr. Bailey, we have studied the structure of the T-cell antigen receptor and immunoglobulin genes in patients with lymphoma. Three important observations have been made. First we have found that in some patients that the structure of the immunoglobulin genes in the tumor cells taken from two different sites could be different. This suggests that two different lymphomas had arisen in the same patient. Second we have found that in general, rearrangement of the T-cell antigen receptor is a good marker of T-cell lymphomas. Finally we have found several cases that were felt to be T-cell lymphomas by cell surface markers but by gene rearrangement were of the B-cell lineage.

Chromosomal Translocation In T-Cell Malignancies

Recurrent chromosome translocations involving the long arm of chromosome 14 are found in T-cell leukemias. In collaboration with Drs. Mak and Lewis we are investigating two patients who have a translocation involving chromosomes 11 and 14. We have demonstrated that the translocation involves the alpha chain of the T-cell receptor. We are in the process of isolating the translocated fragments of DNA.

Haemopoietic Stem Cells

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The continuous production of myeloid and lymphoid cells requires the presence of multipotent stem cells capable of differentiating into mature elements in both of these lineages (Figure 1). Although there is clear evidence for adult mice having a multipotent progenitor capable of producing cells in the myeloid and lymphoid lineages, many of the details of the lineages of differentiation, and in particular, the regulation of these early stem cells remain to be elucidated. Our recent research has involved the development of a model system to analyze differentiation in the haemopoietic system and to characterize the factors which may regulate the growth and development of cells in these lineages. Some multipotent progenitors can be detected by *in vitro* colony assays. However, the stem cells with the highest self-renewal potential can only be identified unequivocally by their ability to reconstitute deficient recipients.

We have concentrated our efforts on reconstituting two recipients with congenital deficiencies of the haemopoietic system. Mice of genotype W/W^v are anemic and can be cured by grafts of normal bone marrow cells; their lymphoid system is normal. Another mutant mouse, *scid*, has no detectable B or T lymphocytes. This mouse, like the W/W^v mouse, can be cured of its immune deficiency by grafts of normal bone marrow cells. The primary advantage of both recipients is that their survival does not depend on their receipt of a graft of normal cells. If the animals are kept healthy, they will survive for well in excess of one year, making it possible to test the differentiative potential of single stem cells. Such an experiment is impossible with lethally irradiated mice whose survival critically depends on the injection of large numbers of multipotent stem cells. With either of the mutants, it is also possible to inject stem cells with limited self-renewal potential and to observe reconstitution of only one lineage in the haemopoietic pathway.

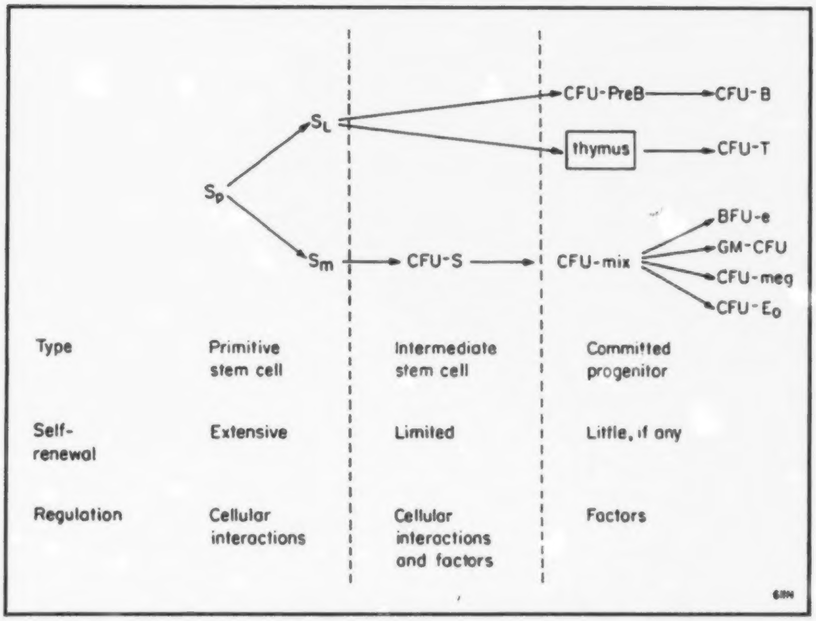

Figure 1. Proposed Lineage Diagram for Haemopoietic System. The most immature stem cells, Sp, Sm and Sn, can only be detected by their ability to reconstitute the haemopoietic system in deficient recipients. CFU-S is a multipotent stem cell with limited self-renewal potential; it can be detected by its ability to form colonies in the spleens of irradiated mice. When given the appropriate growth factors, the committed progenitors for B lymphocytes (B), T lymphocytes (T), erythrocytes (e), granulocytes and macrophages (GM), megakaryocytes (meg) and eosinophils (Eo) can form colonies in tissue culture.

Insertion Of Genetic Markers Into Haemopoietic Stem Cells

Analysis of the differentiative potential of individual cells transplanted into the above recipients requires markers which allow the identification of progeny regardless of their location in the recipient mouse. For this purpose, we have used retrovirus vectors to introduce into haemopoietic stem cells the dominant, selectable bacterial gene for neomycin resistance, neo^r. The neo^r marker allows the *in vitro* selection of cells expressing the newly integrated gene. Most importantly, for the marker experiments, the gene introduced by the retrovirus integrates randomly in the mouse genome. If DNA from cells carrying the neo^r gene is digested with an enzyme which does not cut within the vector, then the size of the junction fragment carrying the neo^r gene will be determined solely by the restriction enzyme sites in the host genome. Thus, the size of the DNA fragment carrying the gene will be characteristic of the integration sites and unique for every cell.

Reconstitution Of W/W^v Mice

We have successfully reconstituted anemic W/W^v mice with stem cells containing the neo^r gene. This result validates our strategy and demonstrates that the neo^r gene can be used as a clonal marker for the most primitive haemopoietic stem cells. By examining DNA in different tissues and in different cells, it is possible to detect common junction fragments which identify cells derived from a common progenitor. In our preliminary experiments, we have confirmed the existence of a multipotent cell capable of giving rise to both myeloid and lymphoid progeny as well as a myeloid restricted stem cell. We also have obtained the first direct evidence for lymphoid committed stem cells.

Insertion Of The Neo^r Gene Into Mature B Lymphocytes

Many studies on the lymphocytes would be facilitated if it were possible to introduce new genetic information into normal B lymphocytes. Retrovirus vectors offer an opportunity to achieve this goal. We have successfully introduced the neo^r gene into normal splenic B lymphocytes. The process is highly efficient with up to 30% of all B cells expressing the new gene.

Reconstitution Of *Scid* Mice

Injection of normal bone marrow stem cells into *scid* mice leads to reconstitution of both the B and T cell deficiencies. Within four weeks detectable numbers of functional B cells and functional T cells are found in normal mice of the same strain. If, however, *scid* mice are exposed to low doses of*scid* ionizing radiation (3.0 Gy) prior to transplantation, reconstitution proceeds rapidly and returns to normal levels of B and T cell function. The reasons for this enhanced reconstitution following radiation are currently under investigation.

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Tumor Biology and Carcinogenesis

Biological Properties Of Malignant Epithelial Cells

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The vast majority (90%) of human cancers are carcinomas i.e they are derived from epithelial tissue. Despite this compelling reason for study, cell and molecular biologists have tended to utilize non-epithelial model systems for studies of carcinogenesis and tumor biology. This program is an attempt to apply molecular and cellular biological techniques to the study of growth control in malignant epithelium.

Stem Cell Differentiation (Buick, Pullano, Till, Ciampi)

Normal epithelia are cell renewal systems; new cells are continually being produced at rates equivalent to cell loss. The cells responsible for the renewal process are termed stem cells. Since tumors almost certainly arise from single, genetically altered stem cells, we have argued that the growth of cell populations within a tumor can best be described as abnormal cell renewal. The implication of this idea is that tumor cell populations will consist of stem and differentiating cells. Since the stem cells are the appropriate target for therapy, it provides the rationale for attempts to understand the characteristics of these tumor stem cells.

We have used tumor cells obtained from malignant ascites of human ovarian carcinoma to test these concepts. By analysing cell differentiation features and the tissue culture clonogenic growth potential of individual cells we have been able to obtain estimates of the size of the stem cell population and a limited amount of information about its biological behaviour. Based on these data, we have constructed mathematical models which seek to explain the properties of tumors in terms of probability functions for cell renewal or differentiation of the tumor stem cells.

Epidermal Growth Factor Receptor (Buick, Filmus, Pollack, Choo, Pullano, Trent)

Epidermal growth factor (EGF) is a peptide hormone which, under normal conditions, plays an important role in the control of cell renewal in a large number of tissues including many epithelia. It mediates its effect through a receptor (EGFR). A great deal of interest has been stimulated by the finding that a portion of the EGFR appears to be encoded by the cellular homologue to the viral *erb-B* oncogene, thus creating a link between cellular growth control and malignant transformation.

Since the EGFR has such importance to epithelial tissue function, we have investigated the receptor and its gene in cell lines derived from breast carcinomas. One line (MDA-468) has been identified which over-expresses the EGFR due to gene amplification. The amplified gene was found to be located in a homogeneous staining region on chromosome 7. Subclones have been selected which had lost this region and as a result have reduced (100x) levels of EGFR. We are using these subclones in comparison to the parent line to assess the mechanism whereby the amplified EGFR gene can provide the cells with a growth advantage *in vivo*.

Future studies in this area will consider the mechanisms whereby abnormalities of the EGFR can cause malignancy by expression of the viral *erb-B* oncogene in normal epithelial cells.

Autocrine Growth Control in Transitional Cell Carcinoma of the Bladder (Buick, Choo, Tannock)

A cell line (HB-10) has been derived from a bladder tumor biopsy. The cells rely on the production of a growth factor for their own proliferation. This type of autocrine mechanism is much studied in fibroblast systems and the HB-10 model should prove useful as an epithelial equivalent. Work is underway to elucidate the molecular structure and mode of action of the growth factor.

Breast Carcinoma Differentiation (Graham, Buick)

The molecular events underlying the differentiation of breast epithelium are poorly understood. In major part this is due to the lack of a tissue culture model for the process. Sodium butyrate has been shown to cause differentiation-like events in cultured breast cancer cell lines. We are studying this process to assess the relevance of the system as a model for breast cell differentiation.

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Chemical Carcinogenesis

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The overall goal of this research program is to provide an experimental basis for understanding mechanisms underlying the biological response to an important class of chemical carcinogens, the nitrosamines. These are valuable compounds with which to study mechanisms of the chemical induction of cancer since they can induce tumors in many organs of numerous species. Additional interest derives from the occurrence of a number of nitrosamines in the environment, and their formation from precursors in the body. Nitrosamines, therefore, are prime suspects in the search for causes of human cancer.

Mechanism Of Tissue Specificity In Nitrosamine Carcinogenesis (Hirani-Hojatti, Mehta, Silinskas, Milligan, Zucker)

A central problem in chemical carcinogenesis is that in addition to variations in strain and species response, the distribution of induced tumors amongst various tissues depends on the type of carcinogen used. The nitrosamines are an unusual class of carcinogen since they can produce tumors in a wide variety of organs. The tissue specificity, although affected somewhat by the dose of the nitrosamine, is not usually affected by the route of administration, and the susceptible tissue depends on the chemical structure of the nitrosamine. The mechanism for this organotropic effect is not understood. The goal of this research project is to investigate the mechanism by which nitrosomethylbenzylamine (NMBzA) specifically induces tumors of the esophagus in the rat, while the structurally related nitrosodimethylamine (NDMA) induces tumors of the liver. These nitrosamines do not concentrate preferentially in the target tissue. Our work has shown that the ability of the esophagus to metabolically activate NMBzA probably plays an important role in determining its carcinogenicity in that organ. In the liver, however, an organ in which NMBzA shows no toxic or carcinogenic effects, we also found extensive metabolic activation of this nitrosamine. Furthermore, NMBzA methylates hepatic DNA and forms the putative promutagenic O^6-methylguanine. Investigation of the potential genotoxic action of NMBzA in the liver, as well as the reasons for the differential cytotoxicity of this nitrosamine in the esophagus compared to the liver, forms the basis of our current research.

Induction Of Pancreatic Cancer By Nitrosamines (Boux, Zucker, Gunhouse, Chan, Giles)

Carcinogenic nitrosamines normally undergo cytochrome P450-dependent α-hydroxylation as a first step in the reaction sequence leading to the production of an electrophilic alkylating agent which interacts with nucleophilic sites in DNA. A somewhat surprising feature of the biological reactivity of several simple nitrosodialkylamines such as nitrosodipropylamine (NDPA) is that in addition to direct transfer of an intact propyl group to DNA, the nitrosamine also acts as a methylating agent. We have found that important intermediates in this process are products of metabolic β-oxidation on one side chain of the nitrosamine, and we have recently succeeded in elucidating the mechanism of the methylation reaction. Our research is now directed towards understanding the mechanism of action of derivatives of NDPA that are oxidized on the β-carbon atoms of both propyl groups. These nitrosamines are unusual in that they induce tumors of the pancreatic ducts in the Syrian hamster. These tumors are particularly interesting because of their similarity to pancreatic cancer in man which is principally ductular in nature.

As well as attempting to determine the mechanism of metabolic activation of these compounds and the mode of interaction of intermediates with DNA, we are using tissue culture techniques, isolated perfused organs, and intact animals to determine the mechanism of tumor initiation in the target cells of the hamster pancreas, and reasons why the rat pancreas is resistant to their carcinogenic action.

Activation of Proto-Oncogenes by Chemical Carcinogens (Hirani-Hojatti, Gunhouse)

Recent research has shown that certain genes which are present in our normal genetic make-up become altered in their structure or expression in cancer cells. Oncogenes of the ras gene family may be activated by single base pair substitutions of their non-transforming counterparts, the proto-oncogenes. Many carcinogens are potent mutagens and much evidence suggests that tumor initiation results from mutations arising from the binding of ultimate carcinogens to DNA. In a new research program, we are investigating whether activated form of nitrosamines can generate transforming oncogenes when they interact with proto-oncogenes, and whether different nitrosamines interact in a site-specific manner with these genes. Such reactions could be important in the initiation of carcinogenesis by nitrosamines and possible in defining their species and organ specificities.

In Vivo Formation of Nitrate, Nitrite And N-Nitroso Compounds (Milligan, Zucker, Ladd)

N-nitroso compounds may form wherever nitrite and organic nitrogen containing compounds (amines, ureas etc.) occur together. Nitrosation reactions are normally favoured by high nitrite concentrations, low pH, and the presence of certain catalysts such as thiocyanate ions. Since sodium nitrite is widely used as a food additive, considerable effort has been devoted to the analysis and characterization of N-nitroso compounds in foods, but conditions for their formation in most foods are not optimal, and levels determined are usually low. The human gastric environment, however, provides conditions that might be expected to favour nitrosation reactions and it is now clear that endogenous formation of N-nitroso compounds does indeed take place. We have recently shown that inhaled nitrogen oxides contribute significantly to man's exposure to nitrate and nitrite. We have also shown that smokers form higher levels of nitrosamines in their bodies than non-smokers. Our current research is to determine the magnitude, duration and route of man's exposure to nitrite or other nitrosating agents, and the extent to which these nitrosating agents result in the formation of N-nitroso compounds in the body.

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Expression Of The Transformation Associated Cellular Protein, p53, In Mammalian Cells

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Many transformed cells express elevated levels of a cellular phosphoprotein of 53,000 daltons that is referred to as p53. p53 has been defined as a tumor antigen because sera from tumor bearing animals including humans often produce antibodies against p53. p53 protein synthesis is regulated in the cell cycle and also appears to play a functionally important role in the progression through the cell cycle. In cells transformed by DNA tumor viruses, p53 forms a complex with two viral tumor antigens - the SV40 large T antigen and the adenovirus Elb-55kd protein. The p53 gene and its mRNA have been cloned and used in DNA transfection experiments to demonstrate a role for p53 in transformation and tumorigenesis.

The objectives of our research are to study the factors that control expression of the p53 gene, to determine the function of p53 in normal cells and to characterize the role played by p53 during cellular transformation. We have chosen three experimental systems in which to examine p53 expression: Friend virus-transformed erythroleukemic mouse cell lines (in collaboration with Dr. A. Bernstein), leukemic blast cells from patients with acute myeloblastic leukemia, AML (in collaboration with Dr. E.A. McCulloch), and cell lines derived from patients with lymphoma (in collaboration with Dr. H. Messner and Dr. M. Tweeddale).

p53 In Friend Virus-Transformed Erythroleukemic Cell Lines (Rovinski, Munroe, Benchimol)

We have observed altered expression of the cellular p53 gene in erythroleukemic cell lines transformed by Friend virus. High levels of p53 protein are found in certain lines, whereas in other cells, p53 protein cannot be detected. Southern blot hybridization analysis indicates that the p53 gene is rearranged and consequently inactivated in cell lines that do not synthesize p53 protein. In addition, we have demonstrated that heterogeneity in p53 gene expression is associated with heterogeneity in tumorigenicity. We are focussing our attention on two independent cell lines that do not synthesize p53 protein as a result of rearrangement in their p53 genes but do synthesize antigenically related proteins of 44,000 daltons and 46,000 daltons respectively. Experiments to clone these rearranged p53 genes and to characterize their gene products are in progress.

p53 Expression In Leukemic Blast Cells Derived From AML Patients (Smith, Benchimol)

Cells from 35 patients were examined for p53 protein synthesis using metabolic labelling with ^{35}S-methionine, immunoprecipitation and polyacrylamide gel electrophoresis. We detected p53 protein synthesis in 20 of these samples but not in the remaining 15.

At the genomic level, the p53 gene appears to be intact and identical in all the cells examined. The possibility that the p53 gene is regulated at the transcriptional or post-transcriptional level is being investigated. We find a significant correlation between the clonogenic capacity of these cells and p53 synthesis and also between the self-renewal capacity of these cells as measured by secondary plating efficiency and the presence of p53.

Studies from Dr. McCulloch's laboratory indicate that only a small proportion of leukemic blast cells have self-renewal capacity. Furthermore, the capacity of blast cells for selfrenewal has prognostic value. We wish to pursue the idea suggested by our work that p53 plays a role during self-renewal. We plan to use expression vectors to introduce the p53 gene into leukemic stem cells in order to ask whether the self-renewal capacity of these cells is affected. We would also like to alter endogenous p53 protein synthesis in order to identify any phenotypic changes that occur.

p53 Gene Expression In Human Lymphoma Cell Lines (Smith, Peacock, Benchimol)

Ten out of eleven lymphoma lines that we have examined express p53 protein. By quantitative radioimmune assay, one of these cell lines has more p53 protein than in SV40-transformed cells. In SV40-transformed cells, p53 forms a complex with the SV40 large T antigen. As a result, p53 protein is stabilized and its half life increases from 20 minutes in the unbound state to over 20 hours in the bound state. p53 is stable in the lymphoma cell line we have examined, and yet it is not bound to T antigen. We would like to determine the mechanism leading to p53 protein stability and accumulation. This lymphoma cell line may provide a good experimental system in which to search for cellular proteins that interact with p53 during establishment and/or transformation.

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Multidrug Resistance And P-Glycoprotein Gene Expression

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Multidrug resistance is a mutation that occurs frequently in human and animal cell lines. It is typified by resistance to a wide variety of structurally and functionally unrelated drugs including major anti-cancer drugs. The occurrence of such a mutation in human tumor cells could result in a therapy-resistant disease. Previous work from this laboratory has identified a cell surface glycoprotein (P-glycoprotein) of 170,000 daltons whose over-expression is closely associated with multidrug resistance in different lines. The objectives of the present research are to investigate the basis of the over-expression of P-glycoprotein in multi-drug resistant cells and to determine whether or not P-glycoprotein over-expression occurs in cancer cells in patients.

Isolation Of A Genetic Probe For The P-Glycoprotein Gene(s)

In order to understand the genetic basis for P-glycoprotein over-expression and the occurrence of multidrug resistance, we undertook to isolate a cDNA specific for P-glycoprotein. This cDNA was isolated using a monoclonal antibody to probe a λgtll cDNA expression library prepared from colchicine resistant hamster cells. Northern blot analysis using one of the cDNAs that was obtained in this matter indicated that this cDNA was homologous to messenger RNAs of the size of 4.7 kilobases. The size of the mRNA is that predicted to code for the P-glycoprotein molecule. In addition, in multidrug resistant cells the amount of mRNAs homologous to this probe increased. All this data indicate that we have cloned a cDNA probe specific for P-glycoprotein messenger RNA. Southern blot analysis showed that the genes for P-glycoprotein were amplified in multidrug resistant cells. Moreover, from the pattern of restriction fragments observed in the Southern blot analysis, it appears that P-glycoprotein is coded for by a family of genes. This is an unexpected finding. It raises the possibility that different but related p-glycoproteins may be involved in generating the complex multidrug resistance phenotype. Further investigations are underway to determine the structure of the P-glycoprotein genes and isolate complete genes of P-glycoprotein in order to determine if transfection into drug sensitive cells could confer drug resistance.

Monoclonal Antibodies Against P-Glycoprotein

Monoclonal antibodies were raised against P-glycoprotein by generating hybridomas prepared by immunizing mice with SDS-solubilize plasma membranes from resistant Chinese hamster ovary and human lymphoid cell lines. Hybridomas supernatants were screened using a panel of plasma membranes immobilized on nitrocellulose filters. By this means, eight monoclonal antibodies were eventually isolated. These antibodies were classified into three groups which recognize three spacially distinct epitopes on hamster P-glycoprotein. One of the monoclonal antibody classes was able to detect P-glycoprotein from human, mouse and hamster cells by Western blot analysis. This monoclonal antibody was used for the cloning of the cDNA specific for P-glycoprotein described above.

P-Glycoprotein Over-Expression In Human Cancers

The availability of the monoclonal antibody allowed us to ask the question of whether or not P-glycoprotein over-expression occurred in human cancers. We initially examined tumor cells from advanced ovarian cancer nonresponsive to combination chemotherapy treatment. From five biopsy samples examined, two samples clearly contained the presence of over expressed P-glycoprotein as detected by our monoclonal antibodies. This and other findings indicate that mutations resulting in multidrug resistance (as detected by P-glycoprotein over-expression) do arise *in vivo* and that such mutations may be a major factor determining response to chemotherapy. Work is now ongoing to determine whether other malignancies also display this P-glycoprotein over-expression. The monoclonal antibodies generated and the probe for the P-glycoprotein genes will be useful for the early detection of multidrug resistant tumor cells. Such early detection may allow for new approached towards treatment of advanced human cancers.

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Radiation Treatment Of Tumors

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The total radiation dose which can be delivered to a tumor during fractionated radiotherapy is limited by the extent of the damage caused by the radiation to the surrounding normal tissues, and it is usually damage expressed late after the irradiation rather than acute damage which is critical. Recent analysis of experimental studies suggests it may be possible to reduce late damage to normal tissues relative to early acute damage by reducing fraction size below the 2 - 3 Gy dose widely used clinically. Implicit in this interpretation is that the effects of radiation which lead to late damage can be repaired to a greater extent following small dose fractions than those which lead to early damage. The influence of such a change in fractionated schedule on tumor response has been suggested to be similar to that of early normal tissue damage but is not well established. If this suggestion is correct it should be possible to achieve a therapeutic gain for radiotherapeutic treatments by reducing fraction size. We have been studying the effect that reducing fraction size has on tumor response.

An important factor affecting the response of tumors to radiation treatment is that they contain radiation resistant hypoxic cells. The influence of such cells is reduced by re-oxygenation during fractionated radiation treatments but the extent of reoxygenation can be affected by the fractionation schedule used. There are certain drugs (hypoxic cell sensitizers) which can sensitize hypoxic cells to radiation without affecting the sensitivity of well-oxygenated cells. These drugs are of considerable interest clinically and one in particular (misonidazole) has been tested in clinical trials and found to have limited efficacy possibly because less than optimal doses had to be used due to toxicity. The combination of such hypoxic cell sensitizers with fractionated radiation doses can be expected to reflect both the sensitizing efficiency of the drug and the extent of re-oxygenation occurring during the fractionated treatment. Our studies have investigated the efficacy of a number of different sensitizers in combination with fractionated treatments.

Fractionated Radiation Treatments

We have examined the response of KHT Sarcomas and RIF1 Tumors growing in C3H mice to treatment with multiple fractions of 1 x 5 Gy per day, 2 x 2.5 Gy per day or 4 x 1.25 Gy per day given with three-hour intervals for various numbers of days. Tumor cell survival was determined using a colony assay after various total doses. The results indicate that, for both tumors, the efficacy of the treatments declines with the size of the dose fractions, consistent with the fact that there is more repair (because of the larger number of fractions) with the smaller doses. This effect appears to be greater than that expected for repair of early normal tissue damage thus these findings suggest that any reduction of late damage obtained by reducing fraction size will be at least partially offset by reduced tumor response. The results further suggest that the effect of changing fractionation schedules on re-oxygenation will need to be considered when assessing any potential therapeutic gain from such an approach.

Hypoxic Cell Sensitizers

We have studied a number of different sensitizers, for their ability to sensitize KHT Sarcomas to radiation treatments with multiple 3 Gy or 5 Gy fractions. Results of these studies indicated that the extent of sensitization was reduced when the smaller fractions were used probably because re-oxygenation reduced the influence of the hypoxic cells on tumor response to the smaller dose fractions. Re-oxygenation was not sufficient however to prevent the hypoxic cells from controlling the tumor response even for 3 Gy fractions.

Misonidazole, desmethylmisonidazole and SR 2508 were the most effective drugs studied in terms of the maximum level of sensitization achieved. This maximum level occurred at administered doses of about 5 mM, too large to be tolerated clinically. At lower drug doses (0.5 - 1 mM) SR 2508 appeared to be less effective (by a factor of about 2 in drug dose) than the other two sensitizers, but this difference is more than offset by the reduced toxicity of SR 2508 relative to misonidazole (factor 3 - 4) suggesting that SR 2508 should be a better drug for clinical studies. Recent studies with a new drug (RSU 1069) which sensitizes at lower doses but is also more toxic than misonidazole, suggest that it gives a greater degree of killing of hypoxic cells than misonidazole at equitoxic doses. The effect however appears to be due not to hypoxic cell radiosensitization but rather to a high degree of direct cytotoxicity of the drug for hypoxic cells. Further studies are in progress to examine the properties of this drug in more detail.

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Retinoblastoma

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Mutations at the RB-1 locus on human chromosome 13 lead to retinal tumors called retinoblastoma. If the mutation at this locus occurs in the germline, then the propensity to develop tumors is transmitted as an autosomal dominant trait. The currently available evidence indicates that tumors develop when both alleles at this locus are inactivated by mutation. In sporadic, non-heritable retinoblastoma, both alleles are inactivated by somatic events. In the heritable form of the disease, one allele is inactivated by a germline mutation while the other is eliminated by somatic events. Individuals carrying the germline mutations have a 95% probability of developing retinoblastoma and usually present with multiple tumors affecting both eyes.

Although the usual tumor occurring in individuals with a germline mutation at the RB-1 locus is retinoblastoma, individuals with this mutation also develop second tumors beginning in the second decade of life. The most common second tumor is osteosarcoma. Recent evidence from another investigator indicates, in fact, that this mutation may result in second tumors in almost 100% of individuals carrying the germline mutation.

The mechanism by which mutations at this locus cause malignant transformation remains unknown. Studies on karyotypic changes in tumors and recent molecular genetic analyses indicate that loss of function results in malignancy. In this sense mutations at RB-1 are different from mutations from known oncogenes where a mutated product is essential for malignant transformation. If total loss of function at RB-1 is responsible for tumor formation, it is likely that the product of this locus is involved in regulation of other genes, either directly or indirectly (e.g. it may code for a receptor). In this sense, malignant transformation results when genes regulated by RB-1 are over expressed or under expressed.

Retention Of The Mutant RB1 Allele In Retinoblastoma

We previously demonstrated that in 70% of retinoblastoma tumors, the majority of the genes on the long arm of chromosome 13 become We postulated that the original mutation, either germline or somatic, became homozygous by the mechanism which generated homozygosity of most genes on chromosome 13. However, in our initial studies we did not have direct evidence that the chromosome carrying the mutation was the one which became homozygous in tumors. By studying retinoblastoma tumors in patients with a family history of retinoblastoma, we have confirmed that the mutant RB-1 allele is retained in tumors. In these families, it is possible, using restriction fragment length polymorphisms, to identify unequivocally which chromosome 13 carries the germline mutation for retinoblastoma. In two families where the mutant chromosome could be identified and where the tumor in one family member showed reduction to homozygosity, the mutant chromosome became homozygous.

Expression Of The N-Myc Oncogene In Retinoblastoma

A detailed analysis of karyotypic abnormalities in retinoblastoma tumors showed that approximately one-third of tumors contain a marker chromosome characteristic of regions of gene amplification. Since the N-myc oncogene has been implicated by others as being important in retinoblastoma, we examined tumors with the abnormal karyotype for possible amplification of the N-myc oncogene. Only one out of nine tumors examined showed N-myc amplification (Fig. 1). We have not yet identified the genes amplified in the other tumors.

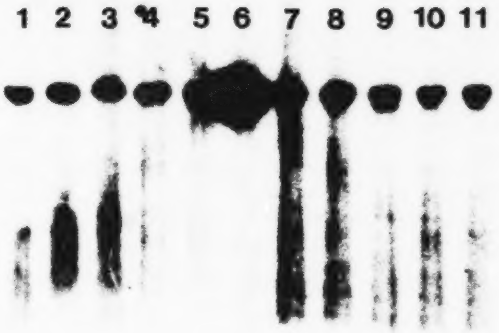

Figure 1. Absence of N-myc Amplification in Retinoblastoma. The figure is a Southern blot of several DNA samples probed with pNb-1. Lane 5 - normal fibroblast DNA, lane 6 - IMR-32 (neuroblastoma with known N-myc amplification), lanes 1 to 4 and 7 to 11 - DNA from retinoblastomas with karyotypic evidence of gene amplification. Not shown is DNA for our retinoblastoma tumor RB355 which has a 50-100-fold amplification of the N-myc gene.

Other investigators have reported very high levels of N-myc expression in retinoblastoma tumor cells and no expression in fetal retina. Our results on N-myc expression do not support this conclusion. We detect N-myc expression in all tumors examined, but the level in some tumors is extremely low and barely detectable. Very high levels of N-myc expression are observed only in tumors with amplification of the N-myc gene. In addition, fetal retinal cells, obtained from 8-10 weeks fetuses, express the N-myc gene. Since the N-myc gene is expressed in embryonic retinal cells from which retinoblastoma tumors develop, its expression in the tumor cannot be considered abnormal.

Role Of The RB1 Locus In Osteosarcoma

As described above, individuals carrying a mutant allele at the RB-1 locus have a high risk of developing osteosarcoma. We have recently examined chromosome 13 in osteosarcoma tumor cells. Like retinoblastoma, a high proportion of tumors show reduction to homozygosity of many genes on the long arm of chromosome 13. Most interestingly, this reduction to homozygosity also occurs in osteosarcoma tumors arising in individuals without the germline mutation at RB-1. Therefore, it is likely that common genetic events initiate both osteosarcoma and retinoblastoma.

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Tumor Progression

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For our research into factors relating to tumor progression, we have developed sublines from a human bladder carcinoma cell line, MGH U1, which have different capacity for tumor formation and metastasis formation in immune deprived mice. These cells are known to have an activated H-ras oncogene and we have sought correlations between the expression of the H-ras oncogene and malignant properties in immune deprived mice. We do not find simple correlations when comparing the average levels of oncogene expression in a population with the overall assessment of its malignant properties. However, this result may be misleading because metastases may depend upon a small subpopulation of cells. To overcome this problem we are currently attempting an alternative approach of introducing oncogenes into the cells and then testing their malignant properties in animals.

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LECTURES AND PAPERS

■ **Alison R.** *Cancer treatment. Living with Cancer Group.* Canadian Cancer Society Oshawa Unit. Oshawa, Ontario, November, 1984.

■ **Alison R.** *Physician's view on self-help.* University of Toronto Medical Students. Toronto, Ontario, March, 1985.

■ **Almeida B (With J Nagai).** *Management of side effects of chemotherapy: A VAB III protocol case study.* Canadian Society of Hospital Pharmacists, Fall Focus 1984. Toronto, Ontario, October, 1984.

■ **Archer MC.** *Endogenous formation of carcinogenic nitrosamines.* Educational Workshop, American Society of Clinical Oncology Annual Meeting. Toronto, Ontario, May, 1984.

■ **Archer MC.** *Oxidative metabolism of N-nitrosomethylbenzylamine by esophageal microsomes.* 6th International Symposium on Microsomes and Drug Oxidation. Brighton, England, August, 1984.

■ **Archer MC.** *Chemical carcinogenesis.* University of Alberta. Edmonton, Alberta, February, 1985.

■ **Arnold L.** *Chemotherapy hazards and complications.* Acute Care Needs of the Patient With Cancer, Clinical Day. Toronto, Ontario, March, 1985.

■ **Benchimol S.** *The p53 tumor antigen: Heterogeneity of expression in friend virus transformed mouse cells.* Ontario/Buffalo Animal Cell and Virus Group Meeting, McMaster University. Hamilton, Ontario, November, 1984.

■ **Benchimol S.** *Rearrangements of the cellular p53 gene in erythroleukemic cells transformed by Friend virus.* Department of Anatomy, Division of Histology, University of Toronto. Toronto, Ontario, February, 1985.

■ **Berger S. (With A. Bernstein)** *Retrovirus shuttle vectors.* Southern Ontario Animal Cells and Virus Group. Hamilton, Ontario, June, 1984.

■ **Bergeron C.** *Update for health professionals: Alzheimer's Disease.* Porcupine Health Unit. Timmins, Ontario, May, 1984.

■ **Bergeron C.** *The Canadian Brain Tissue Bank.* Annual meeting of the Ontario Society of Medical Technologists. Toronto, Ontario, September, 1984.

■ **Bergeron C.** *Role of the pathologists and Brain Bank, and an update on Alzheimer's and Jakob-Creutzfeldt's disease.* Academy of Medicine, Section of Pathology. Toronto, Ontario, March, 1985.

■ **Bergsagel DE.** *Acute phase of plasma cell myeloma.* Progress and Controversies in Multiple Myeloma Symposium. Padua, Italy, April, 1984.

■ **Bergsagel DE.** *Infection in patients with Hodgkin's disease.* XXV Postgraduate Course on Leukemias and Lymphomas: Recent Progress in Diagnosis and Treatment. Milan, Italy, April, 1984.

■ **Bergsagel DE.** *Primary Therapy: Experiences of the NCI-C Myeloma Study Group.* Progress and Controversies in Multiple Myeloma Symposium. Padua, Italy, April, 1984.

■ **Bergsagel DE.** *Role of laparotomy in staging and restaging patients with malignant lymphoma.* XXV Postgraduate Course on Leukemia and Lymphomas: Recent Progress in Diagnosis and Treatment. Milan, Italy, April, 1984.

■ **Bergsagel DE.** *Treatment of plasma cell myeloma.* XXV Postgraduate Course on Leukemias and Lymphomas: Recent Progress in Diagnosis and Treatment. Milan, Itaty, April 1984.

■ **Bergsagel DE.** *Chairman. Bone marrow transplantation and haematologic malignancies.* American Society of Clinical Oncology. Toronto, Ontario, May, 1984.

■ **Bergsagel DE.** *Chairman. Educational workshop: CML, CLL and plasma cell myeloma.* American Society of Clinical Oncology. Toronto, Ontario, May, 1984.

■ **Bergsagel DE.** *Treatment of plasma cell myeloma.* IV Annual Leukemia-Lymphoma Conference, University of South Florida College of Medicine. Longboat Key, Florida, June, 1984.

■ **Bergsagel DE.** *Controversies in the treatment of plasma cell myeloma.* XX Congress of the International Society of Haematology. Buenos Aires, Argentina, September, 1984.

■ **Bergsagel DE.** *Treatment of clinical stage I and II Hodgkin's disease.* XX Congress of the International Society of Haematology. Buenos Aires, Argentina, September, 1984.

■ **Bergsagel DE.** *Evaluating the role of a provincial cancer control program.* Jeffrey A. Gottlieb Memorial Lecture. XXVIII Annual Clinical Conference on Cancer, University of Texas, M.D. Anderson Hospital and Tumor Institute. Houston, Texas, November, 1984.

■ **Bergsagel DE.** *Prognostic factors and the treatment of myeloma patients.* Mead Johnson Lecture, Baptist Memorial Hospital. Memphis, Tennessee, November, 1984.

■ **Bergsagel DE.** *New approaches to resistant and relapsing myeloma.* American Society of Haematology Meeting. Miami, Florida, December, 1984.

■ **Bernstein A.** *Gene transfer with retrovirus vectors.* Baylor College of Medicine,eas Medical Centre. Houston, Texas, April 1984.

■ **Bernstein A.** *Gene transfer with retrovirus vectors.* Immunobiology Research Centre, University of Minnesota. Minneapolis, Minnesota, April, 1984.

■ **Bernstein A.** *Gene transfer with retrovirus vectors.* Department of Pathology, McMaster University. Hamilton, Ontario, September, 1984.

■ **Bernstein A.** *Genomic modification of haematopoietic cells by retrovirus infection.* Department of Biochemistry, McGill University. Montreal, Quebec, November, 1984.

■ **Bernstein A.** *Introduction of new genes into haematopoietic stem cells with retrovirus vectors.* Sloan-Kettering Institute for Cancer Research. New York, New York, November, 1984.

■ **Blend R.** *The impact of newer technologies on the diagnosis and staging of cancer.* Annual Meeting of The Royal College of Physicians and Surgeons of Canada. Montreal, Quebec, September, 1984.

- **Blend R.** *Sonography of the prostate and seminal vesicles.* University of Toronto Refresher Course in Genitourinary Imaging. Toronto, Ontario, October, 1984.
- **Boyd NF.** *Diet and breast dysplasia.* Evidence for the feasibility of clinical trials involving major dietary intervention. Ludwig Institute for Cancer Research. London, England, May, 1984.
- **Boyd NF.** *Controlled trial of dietary intervention in mammary dysplasia.* 11th Semi-Annual Meeting of the Breast Group of the Clinical Oncological Society of Australia. Perth, Australia, June, 1984.
- **Boyd NF.** *Mammographic patterns as risk factors for breast cancer.* 11th Semi-Annual Meeting of the Breast Group of the Clinical Oncological Society of Australia. Perth, Australia, June, 1984.
- **Boyd NF (With ME Cousins, M Beaton, S Bayliss, E Fish and E Fishell).** *Diet and breast disease: Evidence for the feasibility of clinical trials involving dietary fat reduction.* Annual Meeting for the Canadian Society for Clinical Investigation. Montreal, Quebec, September, 1984.
- **Boyd NF (With HJ Sutherland, K Heasman and BJ Cummings).** *Whose utilities for decision analysis?* Annual Meeting for the Canadian Society for Clinical Investigation. Montreal, Quebec, September, 1984.
- **Boyd NF (with W Weber).** *A critique of the methodology used by studies investigating breast cancer risk in benign breast disease.* Biennial International Breast Cancer Research Conference. London, England, March, 1985.
- **Buick RN.** *Stem cell differentiation in human ovarian cancer.* Michigan Cancer Foundation, Seminar Series. Michigan, Detroit, September, 1984.
- **Buick RN.** *Stem cell considerations in human ovarian cancer.* British Association for Cancer Research, Symposium on Clonal Evolution of Tumors. London, England, November, 1984.
- **Buick RN.** *C-myc expression is more related to differentiation and proliferation of HL-60 cells.* American Society for Haematology. Miami, Florida, December, 1984.
- **Buick RN.** *EGF receptor gene amplification in human breast cancer.* Imperial Cancer Research Fund. London, England, March, 1985.
- **Buick RN.** *Stem cell model for human tumor growth.* International Workshop on Chromosomes in Solid Tumors, University of Arizona. Tucson, Arizona, March, 1985.
- **Bush RS.** *The future of radiation therapy (Finzi Lecture).* The Royal Society of Medicine. London, England, April, 1984.
- **Bush RS.** *Ovarian cancer - surgery, radiation chemotherapy.* Radiuumhemmet, Karolinska Institute. Stockholm, Sweden, April, 1984.
- **Bush RS.** *Management of cervical cancer.* "Meet the Professor" presenter, American Society of Clinical Oncology. Toronto, Ontario, May, 1984.
- **Bush RS.** *(i) Cancer of the ovary (ii) Cancer of the endometrium (iii) Cancer of the cervix.* Tomlin Lecture Series. Medford, Oregon, August, 1984.
- **Bush RS.** *Morning summary, non-Hodgkin's lymphoma.* The Ontario Cancer Treatment and Research Foundation Clinical Day. Toronto, Ontario, October, 1984.
- **Bush RS.** *Radiation oncology: Achievement and prospects in gynecologic oncology.* University of Ottawa, IVth Gynecological Oncology Meeting. Ottawa, Ontario, October, 1984.
- **Bush RS.** *Why multifactorial analysis?* (Keynote Speaker). American Society for Therapeutic Radiology and Oncology. Washington, D.C., October, 1984.
- **Canton MD (With D Hinton, RA Phillips and BL Gallie).** *Induction of differentiation in retinoblastoma.* 75th Annual Meeting of the American Association for Cancer Research. Toronto, Ontario, May, 1984.
- **Chen A.** *Community oriented nutritional support of the cancer patient.* Chinese Community Workers and Families of Patients at Mount Sinai Hospital. Toronto, Ontario, May, 1984.
- **Chen A.** *Nutritional considerations of cancer patients.* Telemedicine Audio Teleconferencing program. Toronto, Ontario, January, 1985.
- **Ciampi A (With S Hogy).** *Comparison of three methods for the definition of prognostic strata: cox repression, correspondence analysis and recursive partition.* Orlando Spring Meeting of the Biometric Society. Orlando, Florida, March, 1985.
- **Ciampi A.** *Stochastic processes and cell differentiation.* Department of Mathematical Sciences, McMaster University. Hamilton, Ontario, March, 1985.
- **Clark RM.** *Conservative treatment of breast cancer.* Canadian Cancer Society Meeting. St. John's, Newfoundland, November, 1984.
- **Clark RM.** *A long term study of breast cancer treated by minimal surgery without radiation therapy.* 7th Annual San Antonio Breast Cancer Symposium. San Antonio, Texas, December, 1984.
- **Clark RM.** *Recent advances in cancer.* Canadian Home Office Life Underwriters Seminar. Toronto, Ontario, January, 1985.
- **Clark RM.** *The role of conservative surgery and irradiation in the management of stage I breast cancer.* Hamilton Regional Cancer Centre. Hamilton, Ontario, January, 1985.
- **Clark RM.** *Experiences with conservation therapy in the management of breast cancer.* 5th International Workshop on Combined Therapies in Oncology. Rome, Italy, February, 1985.
- **Clark RM.** *The treatment of early breast cancer: The international experience.* Alternative to mastectomy - The North American experience. Eastern Virginia Medical School and Norfolk General Hospital. Williamsburg, Virginia, March, 1985.

- **Cummings B.** *The influence of histology on the treatment of anal canal carcinoma.* 83rd Annual Meeting of the American Society of Colon and Rectal Surgeons. New Orleans, Louisiana, May, 1984.
- **Cummings B.** *Squamous cancer f the anal canal- multimodality pproach.* Clinical Day in General Surgery, Toronto General Hospital. Toronto, Ontario, June, 1984.
- **Cummings B.** *The treatment of anal canal carcinoma by combined radiation and chemotherapy.* 47th Annual Meeting of the Canadian Association of Radiologists. Vancouver, British Columbia, June, 1984.
- **Cummings B.** *Radiotherapy treatment and results.* Symposium: Current management of oral cancer. 53rd Annual Meeting of the Royal College of Physicians and Surgeons of Canada. Montreal, Quebec, September, 1984.
- **Cummings B.** *Clinical staging of rectal carcinoma.* University of Minnesota. Minneapolis, Minnesota, October, 1984.
- **Cummings B.** *The place for radical radiation in carcinoma of the rectum.* University of Minnesota. Minneapolis, Minnesota, October, 1984.
- **Cummings B.** *Preoperative radiation for rectal carcinoma.* University of Minnesota. Minneapolis, Minnesota, October, 1984.
- **Cummings B.** *Radiation therapy in the treatment of retroperitoneal sarcoma.* 1st Annual Meeting of the American Society for Therapeutic Radiology and Oncology. Washington, D.C., October, 1984.
- **Cummings B.** *Radical radiation therapy for rectal cancer.* St. Luke's Medical Centre. St. Louis, Missouri, November, 1984.
- **Cummings B.** *Radical radiation therapy for rectal cancer.* Washington University. St. Louis, Missouri, November, 1984.
- **Cummings B.** *The treatment of anal cancer.* Mallinckrodt Institute of Radiology at the Washington Medical Centre. St. Louis, Missouri, November, 1984.
- **Cummings B.** *Combined modality therapy for anal cancer.* Kingston Clinic of The Ontario Cancer Treatment and Research Foundation. Kingston, Ontario, March, 1985.
- **Cummings B.** *Combined modality therapy (infusion 5-FU, Mitomycin, radiation) for squamous cell cancers.* Symposium on Continuous Infusion Chemotherapy and Its Interactions with Radiation in the Treatment of Malignant Tumors. Downstate Medical Centre at the State University of New York. New York, New York, March, 1985.
- **Cunningham AJ.** *Relaxation therapy.* Workshop at 5th the Annual Clinical Day of Palliative Care Work Group of Toronto. Toronto, Ontario, May, 1984.
- **Cunningham AJ.** *Coping strategies in cancer patients: biological mediators and clinical implications.* American Psychological Association. Toronto, Ontario, August, 1984.
- **Cunningham AJ.** *Effects of mind on cancer.* The Princess Margaret Hospital. Toronto, Ontario, January, 1985.
- **Cunningham AJ.** *Influence of mind on cancer.* Department of Psychology, Northwestern University. Chicago, Illinois, February, 1985.
- **Cunningham IA (With A Fenster).** *Photo-diode array angiographic system for imaging and blood flow measurements.* Application of Optical Instrumentation in Medicine XII. San Diego, California, February, 1984.
- **Cunningham IA (With BB Hobbs and A Fenster).** *A photo-diode array for angiography and blood flow measurements.* Inter-American Meeting of Medical Physics and the 26th Annual Meeting of the American Association of Physicists in Medicine. Chicago, Illinois, July, 1984.
- **Cunningham IA (With BB Hobbs and A Fenster).** *A new photo-diode array radiograph imaging system for quantitative angiography and blood flow measurements.* 70th Scientific Assembly and Annual Meeting of the Radiological Society of North America. Washington, D.C., November, 1984.
- **Cunningham JR.** *Considerations for interfacing a CT scanner with a radiotherapy department.* Japanese Radiological Society. Matsumoto, Japan, April, 1984.
- **Cunningham JR.** *Structure and Physics of a computerized radiotherapy planning system.* Japanese Radiation Therapy Technicians Society. Matsumoto, Japan, April, 1984.
- **Cunningham JR.** *Calibration of megavoltage photon beams.* American Association of Physicists in Medicine (AAPM). Chicago, Illinois, July, 1984.
- **Cunningham JR.** *Isoresponse and isodose.* Wackato Hospital. Hamilton, New Zealand, September, 1984.
- **Cunningham JR.** *The AAPM dosimetry protocol.* Department of Scientific and Industrial Research (DSIR). Christchurch, New Zealand, October, 1984.
- **Cunningham JR.** *Correction for tissue inhomogeneities in dose calculations for photon beams.* Annual Meeting of the Australasian College of Physical Sciences. Palmerston North, New Zealand, October, 1984.
- **Cunningham JR.** *Dosimetry protocols.* Peter MacCallum Clinic, Melbourne, Australia, October, 1984.
- **Cunningham JR.** *Dosimetry protocols.* Westmead Hospital. Sydney, Australia, Octobor, 1984.
- **Cunningham JR.** *Experience with CT in planning.* Aukland Hospital. Aukland, New Zealand, October, 1984.
- **Cunningham JR.** *Experience with CT in radiotherapy planning.* Atomic Energy of Canada Limited. Sydney, Australia, October, 1984.
- **Cunningham JR.** *Experience with CT in radiotherapy planning.* Peter MacCallum Clinic. Melbourne, Australia, October, 1984.
- **Cunningham JR.** *Experience with CT in radiotherapy planning.*

Westmead Hospital. Sydney, Australia, October, 1984.

■ **Cunningham JR.** *Isoresponse calculations using a radiological model.* Aukland Hospital. Aukland, New Zealand, October, 1984.

■ **Cunningham JR.** *Methods of isodope calculations for electron beams.* Annual Meeting of the Australasian College of Physical Sciences. Palmerston North, New Zealand, October, 1984.

■ **Cunningham JR.** *Calibration of high energy radiation beams.* Radiological Society of North America, Refresher Course. Washington, D.C., November, 1984.

■ **Curtis JE (With HA Messner, R Hasselback and EA McCulloch).** *A clinical trial of high-dose cytosine arabinoside (Ara-C) in acute myeloblastic leukemia (AML): Clinical and laboratory findings.* American Society of Haematology. Miami Beach, Florida, December, 1984.

■ **D'Astous F (With FS Foster).** *Frequency dependence of ultrasound scatter from breast tissue.* Ninth International Symposium on Ultrasonic Imaging and Tissue Characterization. Washington, D.C., June, 1984.

■ **Davidson G (With C Bergeron).** *Parkinson's disease, detentia, and Alzheimer's disease.* 24th Annual Meeting of the Canadian Association of Neuropathologists. Ottawa, Ontario, September, 1984.

■ **Dembo AJ.** *Abdominopelvic radiotherapy in ovarian cancer: A ten year experience.* National Conference of Radiation Oncologists. San Francisco, California, June, 1984.

■ **Dembo AJ.** *Radiotherapy in ovarian cancer.* Grand Rounds, Radiation Oncology Centre of Sutter Community Hospital. Sacramento, California, June, 1984.

■ **Dembo AJ.** *Management of ovarian carcinoma, radiation thetapy of early and advance stages of ovarian cancer.* European Society for Therapeutic Radiology (ESTRO). Jerusalem, Israel, September, 1984.

■ **Dembo AJ.** *A failure analysis in ovarian cancer.* Symposium on Failure Analyses. American Society for Therapeutic Radiology and Oncology. Washington, D.C., October, 1984.

■ **Dembo AJ.** *Radiation therapy in carcinoma of ovary.* Florida Society of Clinical Oncology. Tampa, Florida, October, 1984.

■ **Dembo AJ.** *The role of radiotherapy in endometrial cancer.* Oncology Society of Mayo Clinic. Rochester, Minnesota, October, 1984.

■ **Demmo AJ.** *Radiation therapy in ovarian cancer.* Department of Obstetrics and Gynecology, Queen's University. Kingston, Ontario, December, 1984.

■ **Dembo AJ.** *Radiotherapy — Future directions.* Workshop, Research in Gynecologic Oncology - Cancer of the Ovary, The Princess Margaret Hospital. Toronto, Ontario, December, 1984.

■ **Dembo AJ.** *Radiation therapy in ovarian cancer.* M.D. Anderson Hospital/Texas Medical Centre. Houston, Texas, January-February, 1985.

■ **Dembo AJ.** *Plasma ovarian cancer antigen NB/70K: Clinical Correlations.* Society of Gynecologic Oncologists. Miami, Florida, February, 1985.

■ **Dembo AJ.** *(i) Radiation in ovarian cancer, (ii) Hodgkin's disease: The role of staging laparotomy.* International Conference on Cancer Therapy Trials. Melbourne, Australia, March, 1985.

■ **Dick J (With A Bernstein).** *Gene transfer into haemopoietic stem cells.* Thirteenth Biochemical Genetics Workshop. Park City, Utah, January, 1985.

■ **Dorshkind K (With MJ Bosma and RA Phillips).** *Use of long-term bone marrow cultures and severe combined immunodeficient mice to study B lymphocyte differentiation.* American Association of Anatomists 1984 Meeting. Chicago, Illinois, May, 1984.

■ **Dutton LA.** *Public relations.* OHA Conference for Diagnostic Imaging Managers. Toronto, Ontario, October, 1984.

■ **Dutton LA.** *Public relations in a non-profit organization.* Lecture to marketing students at Seneca College. Toronto, Ontario, March 1985.

■ **Ege GN.** *Application of lymphoscintigraphy in oncology.* Eastern Great Lakes Chapter Meeting, Society of Nuclear Medicine. Niagara Falls, New York, May, 1984.

■ **Ege GN.** *Internal mammary lymphoscintigraphy and breast carcinoma.* St. Barnabas Medical Centre. Livingston, New Jersey, May, 1984.

■ **Ege GN.** *Internal mammary and pelvic lymphoscintigraphy.* Meeting of the European Group of Lymphology. Brussels-Leuven-Liege, Belgium, May-June, 1984.

■ **Enge V (With K Maguire and N Pringle).** *Bone marrow transplant nursing display.* Oncology Nursing Society 9th Annual Congress. Toronto, Ontario, May, 1984.

■ **Enge V (With S. Fenwick).** *The Hickman catheter self-learning program display.* Toronto Health Educators Association. Toronto, Ontario, June, 1984.

■ **Enge V.** *Nursing care of the cancer patient.* Centenial College of Applied Arts and Technology — Registered Nurses Refresher Course. Toronto, Ontario, November, 1984.

■ **Enge V (With S. Fenwick).** *Nursing management of the Hickman catheter.* Victorian Order of Nurses — Metropolitan Toronto Branch. Toronto, Ontario, November, 1984.

■ **Feld R.** *Quality of life and supportive care requirements in patient receiving thepapy for lung cancer.* EORTC Management of Lung Cancer Symposium. Brussels, Belgium, June, 1984.

■ **Feld R.** *Small cell carcinoma of the lung: experience at The Princess Margaret Hospital.* Gustave Roussy Hospital. Villejuif, France, June, 1984.

■ **Feld R.** *Infections in cancer patients.* Tel Hashomer. Tel Aviv, Israel, August, 1984.

- **Feld R.** *Small cell carcinoma of lung: Experience at The Princess Margaret Hospital.* Hadassah Hospital. Jerusalem, Israel, August, 1984.

- **Feld R.** *Small cell carcinoma of the lung: Experience at The Princess Margaret Hospital.* Tel Hashomer. Tel Aviv, Israel, August, 1984 .

- **Feld R.** *CEA: A useful prognostic marker for small cell lung cancer.* 2nd International Workshop on Small Cell Carcinoma. Gleneagles, Scotland, September, 1984.

- **Feld R.** *Neurological complications in patients with small cell lung cancer.* 2nd International Workshop on Small Cell Carcinoma. Gleneagles, Scotland, September, 1984.

- **Feld R.** *Very limited small cell lung cancer: Results of non surgical treatment.* 2nd International Workshop on Small Cell Carcinoma. Gleneagles, Scotland, September, 1984.

- **Feld R.** *VP-16 and cisplatin for small cell lung cancer after failure of induction chemotherapy.* 2nd International Workshop on Small Cell Carcinoma. Gleneagles, Scotland, September, 1984.

- **Feld R.** *Recent progress in the treatment of lung cancer.* Oncology Conference, Notre Dame Hospital. Montreal, Quebec, October, 1984.

- **Feld R.** *Lung cancer.* Grand Rounds, North York General Hospital. Toronto, Ontario, February, 1985.

- **Feld R.** *Infections in the compromised host.* Tri-Hospital Oncology Rounds, Toronto General Hospital, Toronto, Ontario, March, 1985.

- **Fenster A.** *Characteristics of a linear xenon detector array for scanned projection radiographs.* 1984 American Association of Physicists in Medicine Annual Summer School. South Bend, Indiana, July, 1984.

- **Fenster A.** *A new system for quantitative arterial imaging and blood flow measurements.* Digital Imaging Symposium. Hamilton, Ontario, March, 1985.

- **Fenwick S.** *Overview of The Princess Margaret Hospital nursing services.* Oncology Nursing Society 9th Annual Congress. Toronto, Ontario, May, 1984.

- **Fenwick S (With V Enge).** *The Hickman catheter self learning program display.* Ontario Oncology Association — Clinical conference: Cancer Care. Toronto, Ontario, November, 1984.

- **Fenwick S (With V Enge).** *Nursing management of the Hickman Catheter.* Princess Margaret Hospital Education Day for Relief Nurses. Toronto, Ontario, November, 1984.

- **Fitzpatrick J.** *Cancer: The nature of the disease and its treatment.* Canadian Cancer Society. Toronto, Ontario, April, 1984.

- **Fitzpatrick J.** *Management of metastatic cervical cancer from an unknown primary lesion.* International Conference on Head and Neck Cancer. Baltimore, Maryland, July, 1984.

- **Fitzpatrick PJ.** *Multiple cancers in the upper digestive tract.* Epidemiology and Detection, International Conference on Head and Neck Cancer. Baltimore, Maryland, July, 1984.

- **Fitzpatrick PJ.** *Cancer of the lip.* Royal College of physicians and Surgeons of Canada Annual Meeting. Montreal, Quebec, September, 1984.

- **Fitzpatrick PJ.** *Multiple tumors in the upper digestive tract.* Royal College of Physicians and Surgeons of Canada (Canadian Oncologic Society). Montreal, Quebec, September, 1984.

- **Fitzpatrick PJ.** *Magnafield radiotherapy.* Memorial Hospital-Sloan Kettering Centennary. New York, New York, October, 1984.

- **Fitzpatrick PJ.** *Skin cancer and its treatment by radiotherapy.* American Society of Therapeutic Radiologists Refresher Course. Washington, D.C., October, 1984.

- **Fitzpatrick PJ.** *Skin cancer and its treatment by radiotherapy.* Visiting professor, New York University. New York, New York, October, 1984.

- **Fitzpatrick PJ.** *Squamous cell carcinoma of the eyelids.* American Society of Therapeutic Radiologists. Washington, D.C., October, 1984.

- **Fitzpatrick PJ.** *Carcinoma of the lip.* Annual Meeting of the Eastern Great Lakes Head & Neck Oncology Association. Hamilton, Ontario, November, 1984.

- **Fitzpatrick PJ.** *Magnafield irradiation.* The Ontario Cancer Treatment and Research Foundation. Kingston, Ontario, November, 1984.

- **Fitzpatrick PJ.** *Multiple primary tumors in the upper digessive tract.* The Ontario Cancer Treatment and Research Foundation. Kingston, Ontario, November, 1984.

- **Fitzpatrick PJ.** *Panel chairman,* Open Forum. Northeastern Ontario Clinical Day. Sudbury, Ontario, November, 1984.

- **Fitzpatrick PJ.** *Panelist on the treatment of head and neck tumors.* Annual Meeting of the Eastern Great Lakes Head & Neck Onoclogy Association. Hamilton, Ontario, November, 1984.

- **Fitzpatrick PJ.** *Skin cancer and its treatment by radiotherapy.* Northeastern Ontario Annual Clinical Day. Sudbury, Ontario, November, 1984.

- **Fitzpatrick PJ.** *Squamous cell carcinoma of the eyelids.* Annual Meeting of the Eastern Great Lakes Head & Neck Oncology Association. Hamilton, Ontario, November, 1984.

- **Fitzpatrick PJ.** *Squamous cell carcinoma of the eyelids.* Radiological Society of North America. Washington, D.C., November, 1984.

- **Fitzpatrick PJ.** *Twenty years of seeing and treating cancer in Sudbury.* Testimonial dinner by Laurentian Hospital. Sudbury, Ontario, November, 1984.

- **Fitzpatrick PJ.** *Medicine's debt to Radiotherapy.* Hollywood Memorial Hospital. Hollywood, Florida, March, 1985.

- **Foster FS (With E Fishell, B Khodai, K Harasiewicz and JW Hunt).** *Preliminary experience with a prototype ultrasound breast scanner.* 47th Annual Meeting of the Canadian Association of

Radiologists. Vancouver, British Columbia, June, 1984.

■ **Gallie BL (With MD Canton, D Hinton and RA Phillips).** *Modulation of differentiation in retinoblastoma.* Association for Research in Vision and Ophthalmology. Sarasota, Florida, May, 1984.

■ **Gannon, M (With P Tuffnell, G DeBoer, A Dong and C Erlichman).** *Inadequacy of tests to detect absorption of cytotoxic drugs in drug handlers.* Professional Practice Conference of the Canadian Society of Hospital Pharmacists, Toronto, Ontario, February, 1985.

■ **Gorczynski RM (With M Kennedy).** *Associative learning and regulation of immune responses.* 7th Meeting of Canadian College of Neuropsychopharmacology. Halifax, Nova Scotia, May, 1984.

■ **Gorczynski RM (With M Robillard, M Kennedy and MP Chang).** *Age related changes in the allorecognition repertoire of immune T lymphocytes: Evidence for altercation in peripheral expansion (somatic diversifications) of thymus cells.* 16th International Leukocyte Culture Conference. Cambridge, England, August, 1984.

■ **Gorczynski RM (With M Robillard).** *Changes in murine host immune responsiveness after newstyle donor-specific-transfusions occurring alongside alteractions in skin graft survival.* 16th International Leukocyte Culture Conference. Cambridge, England, August, 1984.

■ **Gorczynski RM.** *Conditioned immune responses.* Rochester Medical Centre. Rochester, New York, September, 1984.

■ **Gorczynski RM.** *Psychoneuroimmunology.* Arthritis Health Profession Association Annual Meeting. Toronto, Ontario, November, 1984.

■ **Gorczynski RM.** *Psychoneuroimmunology.* Division of Biological Sciences, York University. Toronto, Ontario, December, 1984.

■ **Gorczynski RM.** *Immunity to L. braziliensis in mice - vaccination strategies.* Connaught Laboratories. Toronto, Ontario, January, 1985.

■ **Gorczynski RM.** *Health, behaviour and immunity.* Department of Biology and Social Sciences, University of Waterloo, Waterloo, Ontario, February, 1985.

■ **Gorczynski RM.** *Regulation of autologous mixed-leukocyte reactions in mice and man.* The Wellesley Hospital. Toronto, Ontario, February, 1985.

■ **Gorczynski RM.** *Regulation of self-nonself discrimination and the development of a functional T-cell repertoire.* University of Michigan. Lansing, Michigan, February, 1985.

■ **Gorczynski RM.** *Occupational stress and immunity.* American Psychosomatic Society Annual Meeting. Washington, D.C., March, 1985.

■ **Gorczynski RM.** *Occupational stress and immunity.* Clinical Research Society of Toronto. Toronto, Ontario, March, 1985.

■ **Greenberg C.** *Nutritional care of the cancer patient.* Ethnic Community Workshop, Toronto, Ontario, October, 1984.

■ **Ha K (With M Minden, N Hozumi and F Galfand).** *Single allelic cμ* gene rearrangement in patient with 7-ALL and AVL. The Japanese Congress for Immunology. Osaka, Japan, August, 1984.

■ **Harwood AR.** *Advances in head and neck cancer.* Ohio State Radiological Society. Cleveland, Ohio, May, 1984.

■ **Harwood AR.** *Whole abdominal irradiation for cancer of the colon.* American Society of Therapeutic Radiologists Meeting. Washington, D.C., October, 1984.

■ **Harwood AR.** *Ionizing radiation. Health effects of physical agents.* Faculty of Medicine, University of Toronto. Toronto, Ontario, January, 1985.

■ **Hasselback R.** *(i) Benign breast disease (ii) Malignancies of the breast.* Nurse Practitioners Association of Ontario. Toronto, Ontario, April, 1984.

■ **Hasselback R.** *Quackery.* CBC Radio Canada. Toronto, Ontario, April, 1984.

■ **Hasselback R.** *Quackery in medicine.* Ontario Society of Radiology Technologists. Ottawa, Ontario, April, 1984.

■ **Hasselback R.** *Effect of a diagnosis of cancer on employment and insurance opportunities.* Canada A.M. Toronto, Ontario, October, 1984.

■ **Hasselback R.** *An introduction to chemotherapy.* Professional Development Day on Service to Cancer Patients for Ethnic Community Workers. Toronto, Ontario, October, 1984.

■ **Hasselback R.** *Macrobiotic diet.* Marketplace. Toronto, Ontario, October, 1984.

■ **Hasselback R.** *Quackery.* Canadian Cancer Society Barrie and District Annual Meeting. Barrie, Ontario, October, 1984.

■ **Hasselback R.** *Chemotherapy.* North Halton Hospice public forum on chemotherapy in cancer treatment and palliative care. Georgetown, Ontario, March, 1985.

■ **Hawley RG (With MJ Shulman and N Hozumi).** *Intracisternal Apartical genes: A family of copia-like transposable elements in mus musculus.* UCLA symposium. Los Angeles, California, April, 1984.

■ **Henkelman RM.** *An optimal imaging sequence for hepatic MRI.* Radiological Society of North America. Washington, D.C., November, 1984.

■ **Henkelman RM.** *Development and evaluation of MRI for oncology.* Cancer Centre of the University of Rochester Medical Centre (Grand Rounds), Rochester, New York, March, 1985.

■ **Hill RP.** *Experimental studies of lung tolerance in relation to bone marrow transplantation.* Joint Centre for Radiation Therapy. Boston, Massachusetts, April, 1984.

■ **Hill RP.** *Host influence on metastases.* Lake Ontario Area Metastasis Group Meeting. Toronto, Ontario, September, 1984.

■ **Hill RP.***In vivo and in vitro methods.* Workshop on Rodent Tumor Models in Therapy

Research. Reisenburg, West Germany, October, 1984.

- **Hill RP (with Farkas-Himsley H).** *Studies of the efficacy of bacteriocin treatment on lung metastases of a murine fibrosarcoma.* Treatment of Metasases: Problems and Prospects. London, England, October, 1984.
- **Hill RP.** *Dynamic heterogeneity and metastasis.* University of Rochester Cancer Centre. Rochester, New York, January, 1985.
- **Hoang T (With MD Minden and EA McCulloch).** *Methylation status of normal and leukemic human DNA, determined by restriction analysis.* Annual Meeting of the American Association for Cancer Research. Toronto, Ontario, May, 1984.
- **Hozumi N.** Department of Immunology and Microbiology, Queen's University. Kingston, Ontario, April, 1984.
- **Hozumi N (with A Ochi, T Hawky, RG Hawky and MJ Shulman).** *Expressiom of cloned immunoglobulin genes.* Workshop on Hybridoma, Canadian Federation of Biological Societies Meeting. Saskatoon, Saskatchewan, June, 1984.
- **Hozumi N.** *Regulation of immunoglobulin gene expression.* Boehringer Manheim Award Lecture. Saskatoon, Saskatchewan, June, 1984.
- **Hozumi N.** *Expression of functional IgM receptor molecules.* The Gordon Research Conference. Plymouth, New Hampshire, July, 1984.
- **Hozumi N.** *Expression of immunoglobulin gene after transfection.* Department of Biochemistry, University of Montreal. Montreal, Quebec, September, 1984.
- **Hunt JW (With A Worthington, G Lockwood, and RP Hill).** *Deep heating using scanning ultrasound devices.* Fourth International Symposium on Hyperthermic Oncology. Aarhus, Denmark, July, 1984.
- **Hunt JW.** *Properties of piezoelectric transducers used for medical studies.* Workshop on Ultrasonic Transducers: Design, Manufacture and characterization. Kingston, Ontario, October, 1984.
- **Hunt JW.** *Theoretical and experimental assessment of focussed ultrasound beams.* Workshop on Ultrasonic Transducers: Design, Manufacture and Characterization. Kingston, Ontario, October, 1984.
- **Japp B.** *The design of eye plaques.* Users Meeting at the American Association of Physicists in Medicine (AAPM). Chicago, Illinois, July, 1984.
- **Japp B.** *Modification of electron beam distributions with "Superflab" bolus.* American Association of Physicists in Medicine (AAPM). Chicago, Illinois, July, 1984.
- **Japp B.** *The clinical use of electrons.* Annual Meeting of The Ontario Cancer Treatment and Research Foundation. Toronto, Ontario, October, 1984.
- **Johns PC (With DJ Drost, A Fenster and MJ Yaffe).** *Dual energy mammography.* American Association of Physicists in Medicine and Inter-American Conference of Medical Physics. Chicago, Illinois, June, 1984.
- **Johns PC (With DJ Drost, MJ Yaffe, A Fenster).** *Investigation of dual-energy radiography for breast cancer detection.* Inter-American Meeting of Medical Physics and the 26th Annual Meeting of the American Association of Physicists in Medicine. Chicago, Illinois, July, 1984.
- **Johns PC (With DB Arnold and MJ Yaffe).** *X-ray characterization of normal and malignant neoplasms in the breast.* Radiological Society of North America Annual Meeting, Washington, D.C., November, 1984.
- **Keane TJ.** *Radiation treatment planning in lung cancer.* Workshop. King's College. Cambridge, England, June, 1984.
- **Keane TJ.** *Panel Member: Staging of head and neck cancer.* International Conference on Head and Neck Cancer. Baltimore, Maryland, June, 1984.
- **Keane TJ.** *Panel Member: The impact of new technology on cancer diagnosis and treatment.* Royal College of Physicians and Surgeons of Canada. Montreal, Quebec, September, 1984.
- **Keane TJ.** *The management of vascular tumors of the head and neck.* American College of Surgeons Annual Meeting. San Francisco, California, October, 1984.
- **Keane TJ.** *Radical radiation therapy with 5-FU infusion and mitomycin C for esophageal squamous carcinoma.* American Society of Therapeutic Radiology and Oncology. Washington, October, 1984.
- **Kukac L (with M Stankovich).** *Nursing management of the Hickman catheter.* Acute Care Needs of the Patient, Clinical Day. Toronto, Ontario, March, 1985.
- **Ling V (with EM Elliott).** *Alpha tubulin genes in CHO cells.* Molecular biology of the cytoskeleton. Cold Spring Harbour Laboratory. Cold Spring Harbour, New York, April, 19884
- **Ling V.** *Mechanisms of drug resistance in cancer therapy.* The 1984 David Pearlman Lecture, University of Wisconsin. Madison, Wisconsin, April, 1984.
- **Ling V.** *Biological basis of cytotoxic drug resistance.* Symposium on the Curability of Cancer, University of Western Ontario. London, Ontario, May, 1984.
- **Ling V.** *Multidrug resistance: Implications for cancer chemotherapy.* Department of Radiation Therapy. University of Texas Medical Branch Hospitals. Galveston, Texas, May, 1984.
- **Ling V.** *Drug resistance.* The Fourth National Cancer Institute of Canada Course in Oncology, McMaster University. Hamilton, Ontario, June, 1984.
- **Ling V.** *Multidrug resistance and metastasis.* Symposium on Mechanisms of Metastasis. Detroit, Michigan, June, 1984.
- **Ling V.** *Genetics of drug resistance. Gordon Research Conferences on Chemotherapy of Experimental and Clinical Cancers. New London, New Hampshire, July, 1984.*
- **Ling V.** *Multidrug resistance and chemotherapy.* International

Conference on Head and Neck Cancer. Baltimore, Maryland, July, 1984.

- **Ling V.** *Drug resistance.* Adriamycin Symposium, Chicago, Illinois, September, 1984.
- **Ling V.** *Genes associated with multidrug resistance.* Maryland Cancer Program on Neoplastic Disease, University of Maryland. Baltimore, Maryland, November, 1984.
- **Ling V.** *Genetics of multidrug resistance.* Department of Medical Genetics. University of Toronto. Toronto, Ontario, November, 1984.
- **Ling V.** *Cancer genetics and drug resistance.* The Henry M. Lemon Symposium on Clinical and Experimental Chemotherapy. University of Nebraska. Omaha, Nebraska, February, 1985.
- **Ling V.** *Drug resistance and chemotherapy.* Ontario Cancer Treatment and Research Foundation Cancer Clinic at Kingston, Queen's University. Kingston, Ontario, February, 1985.
- **Ling V.** *Miltidrug resistance.* Institut du Cancer de Montreal, Quebec, February, 1985
- **McCulloch EA.** *Haemopoietic stem cells.* The John Mithoeffer Visiting Professor, Medical University of South Carolina. Charleston, South Carolina, April, 1984.
- **McCulloch EA.** *The haemopoietic system and its development.* The National Cancer Institute Fourth Course in Oncology, The Ontario Cancer Institute. Toronto, Ontario, June, 1984.
- **McCulloch EA.** *"Where do we go from here?"* General Motors Conference on Cancer Therapy. Jackson Hole, Wyoming, September, 1984.
- **McCulloch EA.** *Acute myeloblastic leukemia: The value of combined clinical and laboratory studies.* Kyoto University. Kyoto, Japan, October, 1984.
- **McCulloch EA.** *Acute myeloblastic leukemia: The value of combined clinical and laboratory studies.* Kyushu Uninersity. Fukuoka, Japan, October, 1984.
- **McCulloch EA.** *haemopoietic stem cells.* 26th Annual Meeting of the Japanese Society of Clinical Haematology. Hagoya, Japan, October, 1984.
- **McCulloch EA.** *Normal stem cells and the clonal haemopathies.* 70th Annual F. Stohlman, Jr., M.D., Memorial Symposium. Boston, Massachusetts, October, 1984.
- **McCulloch EA.** *Stem cells in normal and leukemic haemopoiesis.* University of Tokyo, Tokyo, Japan, October, 1984
- **McCulloch EA.** *Acute myeloblastic leukemia: The value of combined clinical and laboratory studies.* Visiting Professor, Human Oncology Grand Rounds, University of Wisconsin, Wisconsin Clinical Cancer Centre. Madison, Wisconsin, November, 1984.
- **McCulloch EA.** *Exponential growth in culture of blast progenitors from acute myeloblastic leukemia (AML).* 26th Annual Meeting of the American Society of Haematology. Miami, Florida, December, 1984.
- **Mah K (With J Van Dyk and TJ Keane).** *A clinical study to evaluate the dose response of lung tissues to fractionated radiation therapy.* Conference on Optimization in Radiation Therapy. Madison, Wisconsin, September, 1984.
- **Mah K.** *Radiation induced lung damage: The determination of dose response data.* Meeting of Western Canadian Medical Physicist. Thunder Bay, Ontario, March, 1985.
- **Mak TW.** *Genes encoding the human T cell antigen receptor.* Albert Einstein School of Medicine. New York, New York, May, 1984.
- **Mak TW.** *Genes encoding the human T cell antigen receptor.* Cold Spring Harbor Laboratory, Cold Spring Harbor, New York, May, 1984.
- **Mak TW.** *Genes encoding the human T cell antigen receptor.* Columbia University. New York, New York, May, 1984.
- **Mak TW.** *Genes encoding the human T cell antigen receptor.* Department of Microbiology, University of Pennsylvania. Philadelphia, Pennsylvania, May, 1984.
- **Mak TW.** *Genes encoding the human T cell antigen receptor.* Fox Chase Cancer Center Philadelphia, Pennsylvania, May, 1984.
- **Mak TW.** *Genes encoding the human T cell antigen receptor.* Mt. Sinai Hospital New York, New York, May, 1984.
- **Mak TW.** *Genes encoding the human T cell antigen receptor.* New York Medical Centre. New York, New York, May, 1984.
- **Mak TW.** *Genes encoding the human T cell antigen receptor.* Rockefeller University. New York, New York, May, 1984.
- **Mak TW.** *Genes encoding the human T cell antigen receptor.* Massachusetts Institute of Technology. Cambridge, Massachusetts, June, 1984.
- **Mak TW.** *Genes encoding the human T cell antigen receptor.* National Institute of Health. Bethesda, Maryland, June, 1984.
- **Mak TW.** *Genes encoding the human T cell antigen receptor.* Scarborough General Hospital. Scarborough, Ontario, June, 1984.
- **Mak TW.** *Genes encoding the human T cell antigen receptor.* Stanford University. Stanford, California, June, 1984.
- **Mak TW.** *Genes encoding the human T cell antigen receptor.* Canadian Federation of Biological Societies Meeting. Saskatoon, Saskatchewan, June, 1984.
- **Mak TW.** *Genes encoding the human T cell antigen receptor.* Department of Pathology, St. Mary's Hospital Medical School, London, United Kingdom, July, 1984.
- **Mak TW.** *T cell antigen receptor.* Gordon Conference. New Hampshire, Massachusetts, July, 1984.
- **Mak TW.** *T cell antigen receptor.* T Cell Receptor Symposium. Aspen, Colorado, July, 1984.
- **Mak TW.** *Genes encoding the human T cell antigen receptor.* 10th Annual F. Stohlman Jr. M.D.

Memorial Symposium. Boston, Massachusetts, October, 1984.

- **Mak TW.** *Molecular organization of T cell receptor genes.* 34th Symposium on the Biology of Skin. Glenedon Beach, Oregon, October, 1984.
- **Mak TW.** *T cell antigen receptor.* Max-Planck-InstituBtfur Biologie. TuBbingen, Federal Republic of Germany, October, 1984.
- **Mak TW.** *T cell antigen receptor.* American Society of Histocompatibility and Immunogenetics. Miami, Florida, November, 1984.
- **Mak TW.** *T cell receptor.* Case Western Reserve University. Cleveland, Ohio, November, 1984.
- **Mak TW.** *T cell antigen receptor.* National Research Council. Ottawa, Ontario, November, 1984.
- **Mak TW.** *T cell antigen receptor.* University of Minnesota, Minneapolis, Minnesota, December, 1984.
- **Mak TW.** *T cell antigen receptor.* University of Wisconsin. Madison, Wisconsin, December, 1984.
- **Mak TW.** *Structure and function of the α and β chain of the T cell antigen receptor.* National Cancer Institute. Bethesda, Maryland, January, 1985.
- **Mak TW.** *T cell antigen receptor.* Midwinter Symposium of Immunologists. Asilomar, California, January, 1985.
- **Mak TW.** *T cell antigen receptor. UCLA Symposium on Leukemia.* Keystone, Colorado, January, 1985.
- **Mak TW.** *T cell antigen receptor.* European Society of Histocompatibility Meeting. Strasbourg, France, March, 1985.
- **Miller RG.** *Differentiation of cytotoxic T lymphocytes.* Inaugural Symposium. Department of Immunology, University of Toronto. Toronto, Ontario, March, 1985.
- **Miller RG.** *In vitro studies of T cell differentiation.* German Cancer Centre, Heidelberg, West Germany, March, 1985.
- **Miller RG.** *In Vitro studies of T cell differentiation.* Pasteur Institute. Paris, France, March, 1985.
- **Miller RG.** *Rapid changes in specificite within single clones of cytotoxic effector cells.* Conference on T cell differentiation. Ulm, West Germany, March, 1985
- **Miller RG.** *Role of sugars in T cell recognition.* German Cancer Centrer Heidelberg, West Germany, March, 1985.
- **Miller RG.** *Veto cells.* Conference on T cell differentiation. Ulm, West Germany, March, 1985.
- **Miller RG.** *Sixteen two-hour lectures on recent advances in T cell immunology.* Sichuan Medical College. Chengan, Peoples' Republic of China, March-April, 1985.
- **Minden MD.** *Detection of oncogenes.* Research Seminar, University of Toronto. Toronto, Ontario, June 1984.
- **Minden MD.** *Molecular genetics - Its implication for haematology.* City Wide Haematology Rounds, The Hospital for Sick Children. Toronto, Ontario, September, 1984.
- **Minden MD.** *Genetic engineering.* Public Forum on Human Genetic Counselling and Genetic Engineering, National Cancer Institute of Canada, Toronto, Ontario, October, 1984.
- **Minden MD.** *Granulocyte series in marrow: Malignant states - AGL CGL.* Toronto Institute of Medical Technology. Toronto, Ontario, October, 1984.
- **Minden MD.** *Origin of leukemic relapse in BMT detected by restriction fragment length polymorphism.* Great Lakes Meeting, Roswell Park Memorial Institute. Buffalo, New York, October, 1984.
- **Moldovsky H (With RM Gorczynski, FA Lue and E Keystone).** *Interleukins (IL-1 and IL-2) and immune functions during sleep.* 24th Meeting of International Sleep Research Society. Toronto, Ontario, June, 1984.
- **Nishikawa RM (With MH Yaffe).** *Scanned projection digital mammography.* American Association of Physicists in Medicine and Inter-American Conference of Medical Physics. Chicago, Illinois, June, 1984.
- **Ochi A (With RG Hawky, R Tisch and N Hozumi).** *Regulated expression of cloned immunoglobulin genes.* UCLA Symposium. Los Angeles, California, April, 1984.
- **Ottensmeyer FP.** *Energy selecting electron microscopy.* 3rd Pfefferkorn Conference on Electron Optical Systems for Microscopy, Microanalysis and Microlithography. Ocean City, Maryland, April, 1984.
- **Ottensmeyer FP.** *Chromosomes and cartilage: Fine-structure microanalysis using energy lods electrons.* Symposium of the Anatomical Society of Canada. Canadian Federation of Biological Societies Annual Meeting. Saskatoon, Saskatchewan, June, 1984.
- **Ottensmeyer FP.** *Electron energy loss imaging.* Symposium of Microanalysis in Biology, MICRO 84, Annual Meeting of the Royal Microscopical Society. London, England, July, 1984.
- **Ottensmeyer FP.** *Scattered elcytrons in biological structure determination.* NATO Advanced Study Institute on Improved Methods of Examining the Submicron World. Antigonish, Nova Scotia, July-August, 1984.
- **Ottensmeyer FP.** *Energy loss analysis and imaging in biology.* Symposium on Analytical Electron Microscopy. Annual Meeting of the Electron Microscopy Society of America. Detroit, Michigan, August, 1984.
- **Ottensmeyer FP.** *Energy selective imaging of chromatin and cartilage.* High Voltage Electron Microscopy Laboratory, University of Wisconsin. Madison, Wisconsin, November, 1984.
- **Ottensmeyer FP.** *Microanalysis by electron spectroscopic imaging of thin specimens in materials science and biology.* Department of Engineering Physics, Ecole

Polytechnique. Montreal, Quebec, November, 1984.

■ **Ottensmeyer FP.** *Elemental analysis and mapping at high spatial resolutions using energy loss electron spectroscopy.* Department of Engineering Pyysics, Ecole Polytechnique. Montreal, Quebec, November, 1984.

■ **Ottensmeyer FP.** *Elemental analysis and mapping at high spatial resolutions using energy loss electron spectroscopy.* Department of Engineering Physics, Ecole Polytechnique. Montreal, Quebec, February, 1985.

■ **Payne DG.** *Management of choroidal melanoma.* Academy of Medicine. Toronto, Ontario, February, 1985.

■ **Payne DG.** *Radiation therapy of skull base tumors.* WS. Keith Symposium on Skull Base Tumors. Toronto, Ontario, February, 1985.

■ **Payne P (With V Enge).** *Nursing care of the cancer patient.* Victorian Order of Nurses — Quinte Branch. Kingston, Ontario, October, 1984.

■ **Phillips RA.** *Defects in lymphoid differentiation in scid mice.* Department of Tumor Biology, University of Alabama. Birmingham, Alabama, May, 1984.

■ **Phillips RA.** *The inability of primitive haemopoietic stem cells to form colonies in vivo and in vitro.* International Society for Experimental Haematology Meeting. Atlanta, Georgia, August, 1984.

■ **Phillips RA.** *Lymphoid stem cells.* Federation of the American Society for Experimental Biology. Saxon River, Vermont, August, 1984.

■ **Phillips RA.** *Genetic approaches to the study of lymphoid stem cells.* Department of Immunology, University of Toronto. Toronto, Ontario, September, 1984.

■ **Poon P.** *Magnetic resonance and computed tomography scanning of prostatic carcinoma.* American Urological Association, Northeastern Section Seminar. Toronto, Ontario, April, 1984.

■ **Poon P (With M Bronskill, M Henkelman, R Ginsberg and R Feld).** *Magnetic resonance imaging in the detection of mediastinal lymph node metastases in bronchogenic carcinoma.* 47th Annual Meeting of the Canadian Association of Radiologists. Vancouver, British Columbia, June 1984.

■ **Poon P (With RW McCallum, M Heckelman, MJ Bronskill, SB Sutcliffe, M Jewett, WD Rider and A Bruce).** *Magnetic resonance imaging of the prostate.* 47th Annual Meeting of the Canadian Association of Radiologists. Vancouver, British Columbia, June, 1984.

■ **Poon P (With RN Henkelman, MJ Bronskill and GN Ege).** *Optimization of imaging sequences in liver NMRI.* 47th Annual Meeting of the Canadian Association of Radiologists. Vancouver, British Columbia, June, 1984.

■ **Poon P.** *Magnetic resonance imaging.* Telemedicine for Ontario Network. Toronto, Ontario, February, 1985.

■ **Poon P.** *MRI in central nervous system.* Medical Society Meeting, Scarborough General Hospital. Toronto, Ontario, March, 1985.

■ **Poon P.** *MRI in oncology.* Digital Imaging Symposium, McMaster University Medical Centre. Hamilton, Ontario, March, 1985.

■ **Ranelli PJ (With C Bergeron and P Miceli).** *Cerebral amyloid in Alzheimer's disease.* 109th Annual Meeting of the American Neurological Association. Baltimore, Maryland, October, 1984.

■ **Rauth AM.** *The induction and repair of ultraviolet light damage in mammalian cells.* NATO Course on Radiation Carcinogenesis and DNA Alterations. Corfu, Greece, October, 1984.

■ **Rawlinson JA (With AF Bielajew, DM Galbraith and P Munro).** *Theoretical investigation of dose effects due to charge storare insulating phantoms.* American Association of Physicists in Medicine (AAPM). Chicago, Illinois, July, 1984.

■ **Rawlinson JA.** *Electron beam treatment planning methods.* Annual Meeting of The Ontario Cancer Treatment and Research Foundation. Toronto, Ontario, October, 1984.

■ **Rideout DF.** *Paleoradiology.* 47th Annual Meeting of the Canadian Association of Radiologists. Vancouver, British Columbia, June, 1984.

■ **Rideout DF (With R. Blend, PY Poon, S Herman and IF Majesky).** *Factors predicting success or failure in lymphography.* 47th Annual Meeting of the Canadian Association of Radiologists. Vancouver, British Columbia, June, 1984.

■ **Rider WD.** *The contribution of nuclear energy to cancer therapy.* Nuclear Awareness Day, St. Catharines Collegiate and Vocation Schooll St. Catharines, Ontario, April, 1984.

■ **Rider WD.** *Cancer of the oesophagus.* Hamilton Clinic Rounds. Hamilton, Ontario, May, 1984.

■ **Rosen IB (With JA Simpson, SB Sutcliffe and L Gorenstein).** *High dose radiation and the emergence of thyroid nodules desease.* American Association of Endocrine Surgeons. Kansas City, Kansas, April, 1984.

■ **Simpson WJ.** *The impact of radioiodine and external radiation on local control and survival of patients with capillary and follicular thyroid carcinoma.* American Society of Therapeutic Radiology & Oncology. Washington, D.C., October, 1984.

■ **Simpson WJ.** *Practical aspects of treating thyroid cancer and papillary and follicular thyroid cancer: Prognostic factors and management by RAI and RT.* McGill University. Montreal, Quebec, October, 1984.

■ **Simpson WJ.** *(i) Breast cancer - An overview (ii) Thyroid cancer - Prognostic factors and RAI/RT results.* ISRO/WHO sponsored Regional Radiotherapy Education Meeting. Bogota, Columbia, February, 1985.

■ **Squire J (With BL Gallie and RA Phillips).** *Specific chromosonal abnotmalities in retinoblastoma.* 75th Annual Meeting of the American Association for Cancer Research. Toronto, Ontario, May, 1984.

- **Sutcliffe SB.** *Palliative chemotherapy and radiation.* Palliative Care Work Group of Toronto, Annual Clinical Day. Toronto, Ontario, May, 1984.
- **Sutcliffe SB (With MK Gospodarowicz).** *Prognostic groups for management of localised Hodgkin's disease.* 2nd International Conference of Malignant Lymphoma. Lugano, Switzerland, June, 1984.
- **Sutcliffe SB.** *Prognostic groups for management of clinical stage I and II Hodgkin's disease by radiation therapy.* Canadian Haematology Society. Royal College of Physicians, Annual Meeting. Montreal, Quebec, September, 1984.
- **Sutcliffe SB.** *Radiation therapy for clinical stage I and II Hodgkin's disease.* The Ontario Cancer Treatment Foundation, Clinical Day. Toronto, Ontario, October, 1984.
- **Tannock IF.** *(i) Hypoxic cells and chemotherapy (ii) Critical appraisal of the criteria of response in the treatment of malignant disease.* Cross Cancer Institute. Edmonton, Alberta, April, 1984.
- **Tannock IF.** *Critical appraisal of the criteria of response in the treatment of malignant disease.* University of Montrral, Notre Dame Hospital. Montreal, Quebec, April, 1984.
- **Tannock IF.** *The place of chemotherapy in solid tumors of the head and neck.* Toronto General Hospital. Toronto, Ontario, April, 1984.
- **Tannock IF.** *Measurement error and its influence on outcome on cancer management.* London Regional Cancer Centre. London, Ontario, September, 1984.
- **Tannock IF.** Chaired Session on Experimental Chemotherapy Workshop on Rodent Tumors. Frankfurt, West Germany, October, 1984.
- **Tannock IF.** *Chemotherapy that is active against locoregional nasopharyngeal cancer does not prevent or delay metastasis.* Symposium on Treatment of Metastasis: Problems and Prospects. London, England, October, 1984.
- **Tannock IF.** *Bladder cancer: Assessment of response to chemotherapy.* Department of Urology, University of Tennessee. Memphis, Tennessee, November, 1984.
- **Tannock IF.** *Cell death in untreated tumors: Lesions for cancer chemotherapy.* St. Jude Children's Research Institute. Memphis, Tennessee, November, 1984.
- **Tannock IF.** *Implications of tumor heterogeneity for chemotherapy.* Northern California Oncology Group Seminar. Stanford, California, November, 1984.
- **Tannock IF.** *Causes of cell death in tumors.* Yale University. New Haven, Connecticut, December, 1984.
- **Taylor WB (With B Starkoski, MS Paterson and JW Hunt).** *Development of a sonographic breast scanner capable of storing 400 images.* The Canadian Medical and Biological Engineering Conference. Ottawa, Ontario, June, 1984.
- **Thomas GM.** *(i) Carcinoma of the cervix: The Princess Margaret Hospital experience (ii) The implications of the patterns of failure after radiation therapy in cancer of the cervix.* Gynecology Grand Rounds, McMaster Medical Centre. Hamilton, Ontario, April, 1984.
- **Thomas GM (With RS Bush).** *Carcinoma of the cervix.* "Meet the Professor" Session, American Society of Clinical Oncology, Toronto, Ontario, May, 1984.
- **Thomas GM.** *A Phase I-II study of mitomycin, 5-fluorouracil and radiation therapy in poor prognosis carcinoma of cervix.* American Society of Clinical Oncology. Toronto, Ontario, May, 1984.
- **Thomas GM.** *Carcinoma of cervix.* Phase I II study of mitomycin, 5 FU and radiation. Combined Oncology Rounds, Toronto General Hospital. Toronto, Ontario, May, 1984.
- **Thomas GM.** *Mitomycin C, 5 FU and radiation in the treatment of carcinoma of the anal canal.* Piedmont Oncology Association, Winston Salem, North Carolina, July, 1984.
- **Thomas GM.** *Contraversies in the management of seminoma.* City Wide Urology Rounds. The Wellesley Hospital. Toronto, Ontario September, 1984.
- **Thomas GM.** *The implications of the patterns of failure in carcinoma of the cervix after radiation therapy.* University Hospital. Leuven, Belgium, October, 1984.
- **Thomas GM.** *Carcinoma of the cervix.* Epidemiology, Prevention and Treatment, Clinical Day on Disease Prevention. Niagara Falls, Ontario, November, 1984.
- **Thomas GM.** *Adjuvant radiation therapy for breast cancer.* Surgical Rounds, Doctors' Hospital. Toronto, Ontario, January, 1985.
- **Thyssen I.** *Bone marrow transplantation.* Toronto Apheresis Group. Toronto, Ontario, February, 1985.
- **Till JE.** *Quality of life.* The National Cancer Institute of Canada 4th Course in Oncology, McMaster University. Hamilton, Ontario, June, 1984.
- **Till JE.** *Eliciting preferences for alternative treatment in oncology.* 6tt Annual Meeting of the Society for Medical Decision Making. Bethesda, Maryland, November, 1984.
- **Till JE.** *Research on quality of life: some issues.* Institute of Medical Science, University of Toronto. Toronto, Ontario, January, 1985.
- **Tuffnell PG (With G Deboer, A Dong, C Erlichman and M Gannon).** *Screening for toxicity and excretion of mutagens in populations handling chemotherapeutic drugs.* 20th Annual Meeting of American society of Clinical Oncology. Toronto, Ontario, May, 1984.
- **Urbanski SJ (With D McFarlane and NF Boyd).** *Breast epithelial atypia — its significance and correlation with mammographic dysplasia.* Academy of Medicine. Toronto, Ontario, May, 1984.
- **Urbanksi SJ.** *Atypical epithelial breast hyperplasia: diagnosis and significance.* Warsaw School of Medicine. Warsaw, Poland, June, 1984.
- **Urbanski SJ.** *Early gastric cancer.* Warsaw School of Medicine. Warsaw, Poland, June, 1984.

■ **Urbanski SJ.** *Melanocytic dysplasia.* Warsaw School of Medicine. Warsaw, Poland, June, 1984.

■ **Urbanski SJ (With RH Hyland, MA Hutcheon and J Wong).** *Semiinvasive aspergillosis in immunosuppressed patients.* 5th European Congress on diseases of Chest. Lisbon, Portugal, June, 1984.

■ **Van der Vliet V.** *Minimizing adverse drug reactions in the elderly.* Joint Ontario College of Pharmacists — Ontario Pharmaceutical Association Conference. North Bay, Ontario, April, 1984.

■ **Van der Vliet W (With B Almeida).** *ASCO Highlights from ASCO-84.* Canadian Society of Hospital Pharmacists — Pharmaceutical Specialty Group in Oncology. Toronto, Ontario, June, 1984.

■ **Van der Vliet W.** *Cancer patients and their medications.* Service to Cancer Patients for Ethnic Community workers. Toronto, Ontario, September, 1984.

■ **Van Dyk J.** *Total body irradiation: Physical consideration.* First Inter-American Meeting of Medical Physicists (AAPM Refresher Course. Chicago, Illinois, July, 1984.

■ **Van Dyk J.** *Total and half body radiotherapy.* Yale University School of Medicine. New Haven, Connecticut, November, 1984.

■ **Van Dyk J.** *Broad beam absorption of Co-60 gamma rays and 6, 18 and 25 MV x-rays in lead.* Annual Meeting of the Ontario Cancer Treatment and Research Foundation. Toronto, Ontario, October, 1984.

■ **Van Dyk J.** *Dosimetric Concerns in the treatment of Hodgkin's disease — A relief.* Meeting of Western Canadian Medical Physicist. Thunder Bay, Ontario, March, 1985.

■ **Weiler IJ (With MJ Bosma, RA Phillips and RP Perry).** *Evidence for abnormal heavy chain gene rearrangement in scid mice.* Miami Winter Symposium. Miami, Florida, February, 1985.

■ **Whitmore GF.** *Some applications of radiation biology to experimental radiation therapy.* 5th Western Regional Radiobiology Residents Workshop. Edmonton, Alberta, May, 1984.

■ **Whitmore GF.** *Studies on the cloning of human DNA repair genes.* Cross Cancer Institute. Edmonton, Alrerta, May, 1984.

■ **Whitmore GF.** *Oxygen effects in the radiotherapy of solid tumors.* Canadian Federation of Biological Sciences. Saskatoon, Saskatchewan, June, 1984.

■ **Whitmore GF.** *Radiobiology, its role in current and future clinical practice.* 26th Annual Meeting of the American Association of Physicists in Medicine. Chicago, Illinois, July, 1984.

■ **Whitmore GF (With AJ Varghese and S Gulyas).** *Reaction of 2-nitroimidazole metabolites with guanine and their possible biological consequence.* Workshop on the Role of Cyclic Nucleic Acid Adducts in Carcinogenesis and Mutagenesis. Lyon, France, September, 1984.

■ **Whitmore GF.** *The Canadian nuclear fuels waste management program.* The Gray Laboratory. Mount Vernon, England, March, 1985.

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■ **Zucker PF (With AM Chan and MC Archer).** *Cellular specificity in toxicity of pancreatic carcinogens.* American Association for Cancer Research Annual Meeting. Toronto, Ontario, May, 1984.

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The operations of The Princess Margaret Hospital, which is incorporated in The Ontario Cancer Institute, are financed similarly to those of other public hospitals in Ontario, with the exception that additional funds are received from The Ontario Cancer Treatment and Research Foundation.

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Josl Huter was one of the first cancer patients treated at OCI/PMH. Today he is healthy and the owner of Mount St. Louis Moonstone Ski Resort. A ski day at the resort this past winter raised more than $4,000 for the PMH Trust.

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